QUARTERLY REVIEW of MEDICINE

Vol. 6 No. 3 August 1949

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(1) Joslin, E. P.: Postgraduate Med. 4:302 (Oct.) 1948. (2) Kemper, C. F.: Rocky Mountain M. J. 45:1092 (Dec.) 1948. (3) Pollack, H.: New York Med. 4:15 (Dec. 5) 1948.

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QUARTERLY REVIEW of MEDICINE

Vol. 6 No. 3 August 1949

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FOREWORD

THE volume of publications dealing with medical subjects and the number of journals carrying them have become so large that it is impossible for the busy physician to keep abreast of them unaided, even in the single field of internal medicine. The QUARTERLY REVIEW OF MEDICINE is designed to furnish such aid by bringing together in a single publication, as far as possible, brief abstracts of all important current articles bearing on internal medicine and allied specialties, including cardiology and gastroenterology.

The articles are selected from a large number of national and state journals and from many of the more important foreign journals. The abstracts are prepared by workers of the Washington Institute of Medicine working in the Surgeon General's Library and in other libraries in various medical centers. The abstracts are grouped under the following sections:

1. Infectious Diseases
2. Chemotherapy of Infectious Diseases
3. Diseases Caused by Animal Parasities
4. Respiratory Disorders and Diseases
5. Cardiovascular Disorders and Diseases
6. Genitourinary Disorders and Diseases
7. Gastrointestinal Disorders and Diseases
8. Blood and Lymphatic Disorders and Diseases
9. Allergic Disorders and Diseases
10. Deficiency Diseases and Metabolic Disorders
11. Nervous and Muscular Disorders and Diseases
12. Miscellaneous
13. Book Reviews
14. Announcements

The QUARTERY REVIEW OF MEDICINE is designed to keep physicians informed as to current discoveries and advances in internal medicine with a minimum expenditure of time and effort, and to guide them quickly to the original sources if more detailed information is desired.

PAUL W. CLOUGH, M.D.

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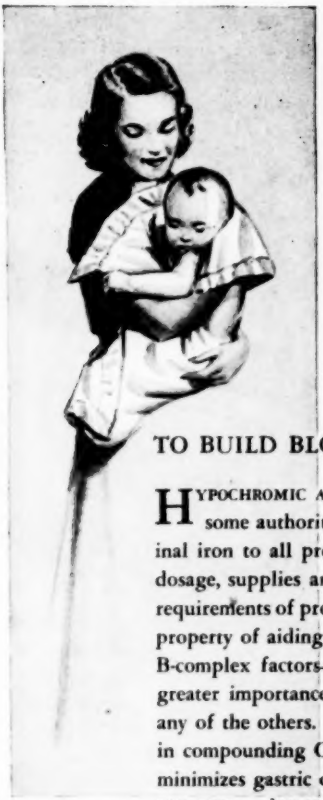

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QUARTERLY REVIEW
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Vol. 6 No. 3 August 1949

1. Infectious Diseases

Common Sources of Error in the Diagnosis and Treatment of Chronic Brucellosis. *Harold J. Harris, Champlain Valley Hospital, Westport, N. Y.* New York State J. Med. 49: 117-80, Jan. 15, 1949.

There is no single laboratory test by which the diagnosis of brucellosis can be made, other than the recovery of the Brucella organism, and this is not always possible in chronic brucellosis. Blood cultures should be made at times when fever is present and at its highest level; if the symptoms suggest local involvement, cultures should be made of such secretions or biopsy materials as are indicated by the localizing symptoms. More than one laboratory test should be used in the diagnosis of chronic brucellosis, including the blood agglutination reaction, the opsonocytophagic reaction, and the intradermal skin test. The intradermal test should be done after the other two tests, as the test may stimulate the production of specific agglutins, or phagocytosis. There may be systemic or focal reactions to the skin test that are exacerbations of previous symptoms, which is of aid in establishing the diagnosis. A staisfactory antigen for the skin test is prepared from heat-killed *Brucella abortus;* other bacterial antigens prepared from each of the Brucella species may be used for supplemental tests. In the clinical study of chronic brucellosis, the possibility of an associated psychoneurosis must be considered; both somatic and psychologic components of the illness may require treatment.

Treatment of chronic brucellosis includes measures to improve the general condition of the patient; antigenic therapy; and chemotherapy and antibiotics. In the general treatment of chronic brucellosis, the diet should be high in protein, moderately high or high in carbohydrate and low in fat; vitamin B and C supplements may be useful to increase phagocytosis and immune response. For specific antigenic therapy, *Brucella abortus* vaccine (bacterin) has brought about recovery in about 50% of cases treated during the last fifteen years. In the past year bacterial antigen complexes (BAC, Hoffmann) has also given promising results. Sulfonamides and streptomycin are less effective in chronic than in acute and subacute brucellosis. However a combination of streptomycin and sulfadiazine may be indicated in severe infections in which other measures fail. Streptomycin should not be continued

after it produces toxic symptoms, especially signs of eighth nerve involvement. Other antibiotics, especially aureomycin, are being investigated with the hope of finding an antibiotic effective against Brucella organisms and less toxic than streptomycin. 21 references.

(Recent work indicates that aureomycin is more effective than sulfonamides and streptomycin in the treatment of severe acute infections. None of the antibiotics has as yet been proved effective in eliminating the infection in chronic cases. Brucellergin is probably the best material available for cutaneous tests, as it is uniform in composition and has little or no antigenic activity, hence does not materially influence subsequent agglutination or phagocytic tests.—ED.)

Studies on Infection with Brucella Abortus Variants. *Werner Braun and Steinar Hauge, University of California, Berkeley, Calif.* J. Immunol. 60: 443-53, Dec. 1948.

Results are presented of a series of studies of infections of mice, guinea pigs, and rabbits with variants of *Brucella abortus*. The variants used were offspring of an isolated single cell previously selected in work on dissociation problems. Survival after infection with different variants was first studied in mice. Deaths occurred shortly after inoculation and were usually the result of a toxic reaction. Homologous and heterologous agglutination tests were made with sera from the 3 host-species. Markedly different agglutination production occurred after inoculation of identical antigens. Previous observations on the independent variation of morphological and antigenic characteristics were substantiated.

Quite different results were obtained after culturing spleens of mice as compared with those from rabbits and guinea pigs. Brucella variants identical with those inoculated, of both nonsmooth and smooth types, were recovered from the spleens of almost all mice infected five weeks before. Only the virulent, smooth type could be recovered from guinea pigs and rabbits, no Brucella organisms being recovered from animals infected with non-smooth variants. These results supported previous in vitro findings of a differential selective action of normal sera from certain species upon establishment of non-smooth types in broth cultures. Difference between antigenic properties of certain variant clones of identical colony type were also found, confirming previous in vitro findings with the acriflavine test. These results prove that species-difference in absence or presence of the selective factor express themselves both in vitro and in vivo. All variants can be recovered from mice because they lack the selective factor which is contained in guinea pig and rabbit sera.

Tests of the effects of antisera from smooth types and several non-smooth variants in mice previously infected with a virulent smooth type showed, on the basis of spleen weights, that infection was most reduced in animals treated with antiserum from an intermediate variant. 9 references. 2 tables.

Characteristics of Septicemias due to *B. proteus*. *(Aspects actuels des septicemies à "Proteus"). E. Benhamou, F. Destaing, G. Barkatz, and A. Sorrel, Algiers, North Africa.* Presse Méd. 56: 789-790, Nov. 13, 1948.

Septicemias due to *B. proteus* are not as rare as was once believed. A present survey of the literature indicates more than 60 cases proven by blood culture. When every fever of unknown origin is studied by blood culture more cases are likely to be discovered.

The source of infection appears to be in the urinary tract in over a third of the cases. In another third the focus of infection seems to be an otitis media. The uterine portal of entry should not be forgotten because recently several cases were observed following induced abortion.

The clinical picture is that of a septicemia with fever, somnolence and dehydration, and untreated cases may die rapidly, within a few days. One of the outstanding clinical characteristics is the very constant and very marked renal involvement with severe nitrogen retention and uremia. The latter supervenes very abruptly and may progress rapidly.

The significance of the renal involvement also becomes apparent in experimental infections induced with this organism in the rabbit. In this animal there is likewise proteinuria, cylindruria and very marked nitrogen retention, often appearing before the bacteremia is otherwise evident.

The prognosis of this disorder has recently changed a great deal. Symtomatic treatment and penicillin therapy were quite ineffective, since most of the isolated Proteus strains are inhibited only by very large amounts of penicillin. Cases treated with 1 million units daily, or more, regularly failed to respond. Streptomycin, however, is effective against many of these strains and should always be given early and in adequate doses (2 Gm. a day or more). With this therapy several cures have been observed.

Immunization against Tetanus in the Allied Armies during World War II. Results. *(La vaccination contre le tetanos dans les armées alliées au cours de la IIe guerre mondiale. Ses résultats.) G. Ramon, Institut National d'Hygiene, Paris, France.* Presse méd. 56: 849-50, Dec. 4, 1948.

It was suggested first in 1924 that the effectiveness of tetanus toxoid should make this material particularly suitable for the prevention of tetanus in military personnel. Shortly thereafter, the use of combined tetanus and diphtheria toxoid was introduced in the French army and was made compulsory in 1936. In the course of the hostilities of 1940 there was only a limited number of wounded in the French army, but among them was not a known case of tetanus until the fall of France.

The British army introduced tetanus (2 injections of 1 cc. of fluid toxoid each at a 5 week interval) in 1939, and in 1942 a booster dose of 1 cc. at the end of one year was likewise administered. On the western front there occurred 6 cases of tetanus among 103,000 wounded British soldiers. Three of these individuals definitely had been vaccinated; in the other 3 immuni-

zation from tetanus could not be ascertained. Among a small number of German prisoners wounded in the same area, there were 25 cases of tetanus. If the incidence of tetanus in the first and second World Wars in the same areas is compared, the incidence was 1.5 per 1,000 wounded in 1914 to 1918 when antitoxin only was used, against 0.06 per 1,000 wounded in 1940 to 1945, with the application of toxoid.

In the American army administration of tetanus toxoid was compulsory after the beginning of mobilization in 1940. Three doses of 1 cc. of fluid toxoid were given to all soldiers at three week intervals. A booster dose was administered at the end of one year or prior to leaving for active combat. If wounded they received an additional booster injection of toxoid, but not antitoxin. It was observed in many provincial French hospitals in the combat zone that among approximately equal numbers of American and German casualties tetanus appeared with some regularity among the latter, never among the former. It is known that the soil of Normandy is especially rich in tetanus spores, and the number of cases among the non-immunized Germans served as control for the efficacy of immunization with toxoid. At the end of hostilities there had been only 12 cases of tetanus among more than 10,000,000 soldiers in the United States army (largely immunized with toxoid). The few that escaped immunization accidentally furnished 6 of the 12 cases of tetanus, the remainder occurred in soldiers who had received toxoid.

In view of this enormous experience it must be concluded that immunization with tetanus toxoid is one of the most effective means of immunizing from preventable disease known at present. Its widespread use in peace time also must be urged. 26 references.

The Intradermal Mecholyl Test for Anidrosis; a Diagnostic Aid in Leprosy. *Harry L. Arnold, Jr., The Clinic, Honolulu, T.H.* Internat. J. Leprosy, N. Orleans. 16: 335-46, July-Sept. 1948.

A simple and easily performed method of testing for leprotic anidrosis is described. Acetylcholine is the chemical mediator of the sweat glands, and they normally respond directly to it upon injection. Metacholine or its chloride have the same effect upon sweat glands as acetylcholine or its chloride. It was demonstrated, however, that the denervated sweat glands did not respond to intradermal injections of metacholine. It therefore appeared that the anidrosis of leprous skin lesions was caused by a leprous neuritis, probably of the postganglionic sympathetic nerve fibers. Denervation of sweat glands probably occurs early in tuberculoid leprosy in the skin and eventually when nerve trunks are involved by leprosy of either type.

The metacholine sweating test is performed by injecting 0.05 to 0.1 cc. of a 1% aqueous solution of metacholine chloride intradermally at the border of the lesion so that the wheal is partly within and partly outside the involved area. The lesion and adjacent normal skin are first painted with Minor's solution. An additional injection within and another without the lesion may be

made in larger lesions. The droplet of solution which leaks back is gently blotted off and the entire area lightly dusted with powdered starch. Sweat droplets commence appearing in a few seconds at the mouths of still functioning sweat glands and turn the iodine-starch combination over the area a deep blue-black which remains. This sweat secretion spreads over a concentric area with a radius of 1 to 3 cm. about the intradermal wheal. A maximum response develops in two or three minutes. Responses are recorded as negative, doubtful or positive. A response is negative when no sweat droplets are seen in the tested area and doubtful when only 6 or 8 pinpoint-sized droplets appear. Otherwise it is positive. It has been found that results of this test may be recorded with assurance in contrast to the histamine test which is so uncertain as to be practically useless in dark-skinned patients. No great difference in results was found in the metacholine test when made with 1:100 or 1:20,000 dilutions, but the former is preferred for routine testing.

This test is considered to indicate leprosy when positive, and there is no equally good evidence to the contrary. 19 references. 2 tables.

Erythema Nodosum Seen with Primary Tuberculous Infection under Sulfathiazole Therapy. *(Erythème noueux du sulfathiazol et primo-infection tuberculeuse. A propos de deux observations.) A. Lemaire, J. Loeper, C. Koupernik, Paris, France.* Progres méd. 76: 149-150, April 10, 1948.

The appearance of erythema nodosum in the course of treatment with the sulfonamides, particularly sulfathiazole, is well known. The frequency of this occurrence has been variously estimated at 8--28%. Similarly, the appearance of erythema nodosum in the course of primary tuberculous infection is a frequent phenomenon. It is uncommon, however, to see these two varieties apparently combined, with the skin rash appearing in the course of a tuberculous primary infection, apparently precipitated by sulfathiazole therapy. Two such cases are reported.

Both were young adults whose presenting symptoms were chilliness, fever, and increasing fatigue. Respiratory symptoms then appeared followed by some thoracic pain, and the signs of pleural effusion. Upon the appearance of phlyctenular conjunctivitis in one individual with a positive tuberculin reaction the patient was given 3 Gm. of sulfathiazole. Twenty-four hours later there was widespread erythema nodosum, persisting while the sulfonamide administration continued for 3 days, and disappearing within 48 hours of its withdrawal.

The other patient had a pharyngitis in addition to the symptoms mentioned above, and throat culture revealed many hemolytic streptococci. He was placed on sulfathiazole in full doses by mouth and a tuberculin test was applied. The latter was negative at first, but within 24 hours of sulfonamide therapy erythema nodosum appeared, lasted for 3 days, then disappeared while the drug was still being given. The next day the tuberculin reaction became positive.

Over-all statistics of the incidence of erythema nodosum were as follows: Among 788 tuberculin-negative individuals treated for various febrile illnesses 8, or 1% developed typical lesions. In 135 cases of primary tuberculous infection, not treated with sulfonamides, the incidence was 34.5%. In 25 individuals with primary tuberculous infection who also received sulfonamides, the incidence was 68.6%.

These figures and reported cases indicate the high degree of probability of eliciting erythema nodosum in individuals with primary tuberculous infection by treatment with one of the sulfonamides, especially sulfathiazole. 8 references.

Complications of Vaccination Against Smallpox. *Morris Greenberg, New York, N. Y.* Am. J. Dis. Child. 76: 492-502, Nov. 1948.

In March 1947, a small outbreak of smallpox occurred in New York City, in which there were 12 cases, with two deaths. Since many people had been exposed, vaccination was urged on all residents, and in a period of a month more than 5 million people were vaccinated. This offered an opportunity to study complications resulting from vaccination.

There were observed 45 cases of postvaccinal encephalitis, a ratio of 1 case to 110,000 vaccinations. This is a much smaller ratio than in the experience of England and Holland where most of the cases have been reported. The onsets were usually abrupt, with fever, headache, vomiting and confusion; in the mild cases dizziness, irritability and ataxia were common; in the severe cases there were disorientation, aphasia, delirium, convulsions, stupor and coma. Signs of meningeal irritation with moderate pleocytosis in the spinal fluid were usual, and paralyses of the extremities were not uncommon. In spite of the severe symptoms, recovery was the rule in one to two weeks. Four deaths were recorded, and all were autopsied. The typical pathologic picture of postinfectious encephalitis was not found in any. In the English and Dutch cases the mortality is reported to be 30 to 50%.

Generalized vaccinia was seen in 45 cases. In 15, vaccinia virus was recovered by growth on chick embryo; in the others, this was not attempted. More than three-fourths of the cases were in children under 5 years of age, a third in infants under one. All but 7 had a preexisting eczema. Only 17 had been vaccinated; 27 had not been vaccinated but had been in contact with a recently vaccinated person, and one had had no such contact.

Frequently seen were regional lymphadenopathy; occasionally seen were non-specific generalized macular and urticarial lesions and localized infections, such as impetigo. Only one serious infection occurred; this was in an individual of 66 who was vaccinated on the left arm. A cellulitis of the arm developed, which spread to the chest and back. He developed a septic fever and died with a diagnosis of sepsis and bronchopneumonia. Not a single case of tetanus occurred.

False positive serologic reactions for syphilis were obtained in 9% of a small group of vaccinated non-syphilitic individuals. A battery of four tests was used, and in only one instance were all four positive.

Preliminary data of a study of 2,800 infants born to women who had been vaccinated in the first four months of pregnancy and a control group of 2,000 infants born at the same time to women who had not been vaccinated indicated no increase in the ratio of congenital defects of the vaccinated as compared to the control group.

A sampling of about 25,000 vaccinated individuals who returned for readings indicated that about three quarters of them had successful primary or accelerated takes. This indicates a high degree of susceptibility to smallpox in the sample surveyed. 18 references. 6 tables.—*Author's abstract.*

Vaccination Against Smallpox and the Serologic Test for Syphilis. *(Vaccination jennerienne et réaction de Wassermann). V. de Lavergne, J. Watrin and J. Auchois, Nancy, France.* Progres méd. 77: 123-124, March 24, 1949.

It has been known for some time, particularly since the work of Barnard in 1940, that vaccination against smallpox may result in a "false positive" serologic test for syphilis. In the individual private patient this fact is of some significance, but provided the physician is aware of a recent vaccination, it is of little importance.

The situation is different, however, when public health authorities are attempting to deal with large groups of people such as military personnel, and more recently camps of displaced persons, seasonal workers, etc.

Past experience has shown that from 10 to 18% of persons with negative serologic tests for syphilis develop positive reactions after vaccination. The majority of these positives are very weak, and only about 5 per cent may be definite enough to cause error or doubt in the diagnosis. Ordinarily false positives are said to appear within 5-15 days after vaccination, and last only a short time. Most of the false positives will have returned to negativity in from a few weeks to 3 months. It has been observed frequently that the change in serologic reaction is quite independent of the degree of apparent reaction to vaccination. False serologic positives may appear as often after immune reactions as after primary takes. It is likewise well accepted that these positive reactions are more frequently detected with the flocculation than with complement fixation tests.

Since 1947 large groups of Italians have come to work in French factories. Most of these individuals had never been vaccinated against smallpox and had never had any serologic for syphilis performed. All newly arrived persons at one center were screened by serologic tests and subsequently were vaccinated.

Among 9,842 sera submitted to the laboratory and examined by eight different serologic tests for syphilis, 144 or 1.4% were positive. About one month after the laborers had been vaccinated 108 were reexamined by means

of the same serologic tests. Nineteen, or 17% then gave positive serologic reactions, while having been negative prior to vaccination. Of the 19 individuals with "false positive" serologic tests, 14 could be re-examined between the 31st and the 115th day after vaccination. In all but 3 the serologic test had returned to normal without any antiluetic therapy having been administered. The remaining 3 positives were once more checked and 2 likewise had returned to negativity while the third still had a strongly positive Kahn test on the 107th day after vaccination, but a negative reaction on the 167th day.

The experience here reported essentially agrees with other findings and emphasizes the necessity of strongly considering the possibility of a false positive reaction if found in an individual without history or findings of lues within a short time after smallpox vaccination. In the daily practice of medicine this is of particular importance in the evaluation of serologic tests for syphilis performed in the course of premarital examinations. There the false positives encountered after vaccination have to be considered with greatest care to avoid disastrous psychological effects on the individuals to be married and their families. Repeated tests are essential and a single test should never form the basis for a positive diagnosis of lues or indication for treatment.

The Problem of Poliomyelitis Orientation of Research. *(Le problème de la poliomyelite et l'orientation des récherches) P. Lepine, Pasteur Institute, Paris, France.* Presse méd. 57: 2-3, Jan. 1, 1949.

Since the first isolation of the virus of poliomyelitis in 1909 an enormous amount of research has been performed in that field. Nevertheless the problem of that disease is far from solved. It appears to become more widespread every year, and the number of recognized cases increases steadily. Only intensive and systematic research offers hope for even a partial understanding of this disease and its behavior.

Some of the more important problems in research can be grouped around the following questions:

1. Method for the biological detection of the poliomyelitis virus.
The only animal uniformly susceptible is the monkey — which is expensive and impractical. A few strains are adaptable to rodents, but the majority are not. A better biologic test would be of prime importance.

2. Factors determining the neurotropic behavior of the virus.
The overwhelming majority of individuals who acquire the virus do not develop signs and symptoms of central nervous system damage. It is known that some metabolic abnormalities, e.g., thiamine deficiency, engender resistance in some animals. It will be necessary to determine more of the factors responsible for resistance or susceptibility of the nervous system.

3. The relationship between specific antibodies in the serum and immunity to the disease.

The great majority of all adults possess antibodies capable of neutralizing certain strains of poliomyelitis virus. However, it is known that the presence of these antibodies does not protect these individuals from coming down with poliomyelitis, nor does serum containing such antibodies offer passive protection to others. Some of these results can be explained by strain-specificity of antibodies. However, one wonders whether these antibodies perhaps represent merely the response to the presnce of an antigen (a virus) in the intestine, without implying previous infection.

4. The immunologic (antigenic) structure of the virus of poliomyetitis.
It is well established that several groups of viruses exist, able to produce the clinical picture of poliomyelitis, but differing in the ability to infect other hosts, e.g., rodents. Their antigenic differences are borne out by cross-immunization and cross-infection experiments. Whether such antigenic differences bear any relation to epidemic behavior is uncertain.

5. Search for a specific therapeutic agent.
To date no useful agent has been discovered either to prevent or to modify the course of poliomyelitic infection in man. The measures that have found application are largely palliative and directed toward the late effects of the disease. Intensive work is necessary to determine whether any of the leads obtained in animal work can be applied to patients.

6. The question of vaccination.
There is as yet no method available permitting inoculation for the purpose of inducing immunity. One of the main problems in experimentation in this direction is the great difficulty of obtaining large quantities of virus. Altogether there is little hope for the development of an effective prophylactic for this disease.

The most hopeful approach to the problems of poliomyelitis lies in an extensive comprehensive program for research, and in close collaboration between laboratory and clinic. 3 references.

Tracheotomy in Poliomyelitis Simplified with New Respirator. *R. L. Peterson and R. C. Ward, Boise, Idaho.* Arch. Otolaryng. 48: 156-48, Aug. 1948.

The lifesaving effect of tracheotomies on certain types of poliomyelitis patients has been well established. Tracheotomies that have been performed on patients with severe respiratory paralysis, in conventional type tank respirators, have been difficult. The established technic has been to open the respirator, to give the patient artificial respiration if necessary, and to do a tracheotomy as rapidly as possible. In the authors' experience in the Idaho epidemic and also in data reported from other epidemics, this technic has been carried out with considerable difficulty and sometimes has resulted in severe anoxemia and cardiac strain for the patient. After tracheotomy, considerable difficulty has been encountered in the care of the tracheotomized patient in the tank type respirator.

Previous so-called lung respirators have not been practical for tracheotomy, because of the tight fitting collar. A new respirator of this type has been developed by J. J. Monaghan of Denver. This respirator does away entirely with the neck piece. It in no way interferes with the technic of regular tracheotomy done over a properly placed bronchoscope. The head is freely movable and postoperative care is simplified.

It has been the authors' privilege to use this new type respirator and in their hands, it has greatly simplified the operation of tracheotomy on respirator cases. 4 references. 1 figure.—*Author's abstract.*

Clinical Features of a Summer Disease (Three-Day Fever) Apparently of Virus Etiology. *C. H. Webb and S. Geo. Wolfe, Children's Clinic and Vierre Simpson, Caddo-Shreveport Health Unit, Shreveport, La.* New Orleans M. & S. J. 101: 249-56, Dec. 1948.

Forty typical and 8 possible cases of a presumably new infectious disease, appearing in endemic form among children and clinically termed "Three-day Fever," were studied during the summer of 1947. A similar brief endemic occurred in 1946.

Striking features of the disease were sudden onset of moderate to high fever, severe headache, often myalgia, and the general absence of respiratory or gastrointestinal symptoms. Duration of fever was 3 days in 60% of cases, with rapid recovery. No complications were noted. Physical findings were minimal: moderate injection of the pharynx, pulse and respiratory rates increased in proportion to the temperature, and minimal prostration accompanying hyperpyrexia.

Results of routine laboratory tests suggested a non-bacterial etiology. Leukocyte counts were normal to low, less than 10,000 cells per cu. mm. in every instance. Differential counts varied; in 4 instances of a total of 15, atypical or "Beta" lymphocytes appeared toward the latter part of the illness. Spinal fluid study was normal in two children who exhibited stiff neck or back.

A limited epidemiological survey pointed toward person-to-person mode of spread, with incubation period of four to seven days. The disease does not seem to be highly contagious, less so among adults than children. At the time of this endemic, other diseases of known viral etiology were at low ebb in the city, and the cases described were not thought to be mild attacks of known diseases. For these reasons, and in view of failure to respond to antibiotic or sulfonamide therapy, "Three-day Fever" is suggested as one of many ill-defined childhood infections due to viral agents.

In an addendum the authors call attention to an article by Howitt, Bishop and Kissling (*Am. J. Pub. Health*, 38: 1263, Sept. 1948) from the U. S. Public Health Laboratory, Montgomery, Ala., suggesting on the basis of serum neutralization tests that the virus of pneumoencephalitis of fowls (Newcastle's disease) is the etiological agent responsible for endemics of a

similar illness occurring among children and occasionally adults in Tennessee and Alabama during 1947 and 1948. Laboratory personnel working with the virus exhibited change from negative to positive serum neutralization tests after developing an influenza-like illness.

Sera from one child in the authors' series and from 3 of 5 children having a similar illness in 1948 showed positive neutralization tests. Conclusive proof by isolation of the virus from a case of "Three-day Fever" has not been accomplished. 5 references. 1 figure. 4 tables.—*Author's abstract.*

The "Yes" and "No" of Nutrition and Natural Resistance to Infectious Disease. *Howard A. Schneider, Ph.D., Rockefeller Institute for Medical Research, New York, N. Y.* Am. J. Pub. Health. 39: 57-60, Jan. 1949.

Natural resistance to infectious disease means that the disease does not develop in a prospective host even when encountered for the first time. Some species are naturally resistant to a disease to which other species are susceptible. Human beings are susceptible to measles but mice are not. This difference seems in some way connected with the genetic basis for the difference between mice and men, and is called the interspecific difference. This is not, however, affected by diet. There are also marked individual differences in susceptibility to a given pathogen and this may be either genetic or environmental.

Even environmental agents such as diet act within a genetic framework. Experimental examination of the different genetic circumstances in which host and pathogen can meet, to determine if and when diet can affect natural resistance, must consider the genetic factors in both host and pathogen. There are 3 great classes of hosts and 3 of pathogens. When these meet, there are 9 instances which diet may affect. A table is presented showing that no dietary effect occurs in 8 of the 9 instances. Diet, therefore, does influence natural resistance, even though in only 1 of 9 instances. In this single instance however, genetically heterogeneous hosts were infected by mixed populations of virulent and avirulent pathogenic bacteria. This is what actually occurs in life. The single instance is therefore more important than it at first appeared, because it represents the experience of most of the natural world. Diet then influences natural resistance more than it does not. Using the specific example of mice and mouse typhoid, it has been found by experiment that the germ of whole wheat is the dietary agent responsible for increased survivorship. This is probably a new nutritional entity, as no nutrients thus far recognized, including all known vitamins, can replace its effects. Efforts are now being made to isolate and identify this compound. 3 references. 1 table.

Mumps Complicated by Myocarditis, Meningoencephalitis and Pancreatitis. Review of the Literature and Report of a Case. *John H. Bland, University of Vermont College of Medicine, Burlington, Vt.* New England J. Med. 240: 417-19, Mar. 17, 1949.

Mumps is usually considered to be an acute systemic disease of specific viral etiology with a special predilection for the parotid glands. However, it

becomes more and more apparent that the virus of mumps may produce pathologic change in any sort of tissue. Myocarditis has until recent years been considered a rare and unusual complication. A case is presented as additional evidence to support the belief that mumps is a generalized infectious process, and that the myocardium and pericardium may be involved by an acute infectious process of viral etiology occurring with varying frequency and of varying severity. A review of the literature discloses that 15.4% of all instances of hospitalized mumps cases present electrocardiographic evidence of myocarditis. Only rarely is there clinical evidence of this complication. No specific electrocardiographic pattern has been noted. A prolongation of the PR interval has been noted regularly in the cases reported, and has also been noted in the instances of other acute infectious diseases, such as pneumonia, scarlet fever, diphtheria and measles. It is suggested that the PR interval changes seen in rheumatic fever may no longer be considered a specific change.

A case of mumps in a 55 year old man was reported. Patient developed in the following sequence—myocarditis, meningoencephalitis, pancreatitis and finally the typical parotitis. He had an uneventful convalescence and was seen six months following his discharge, at which time there was no suggestion of sequelae. All evidence of clinical and electrocardiographic myocarditis had vanished.

The importance of recognizing mumps myocarditis is stressed because with the knowledge of its presence one is more inclined to prolong the convalescence to prevent the occurrence of myocardial residue in the event of extensive involvement. Apparently there are no residua and the process is completely reversible in the vast majority of cases, though reversal may be delayed by failure to recognize its presence.

The complement-fixation test and intradermal skin test of Enders is suggested as a diagnostic aid in an obscure myocarditis. Literature on this subject is reviewed and electrocardiographic study when possible is recommended in all infectious diseases. 13 references.—*Author's abstract.*

2. Chemotherapy of Infectious Diseases

An Advance in the Chemotherapy of Tuberculosis. *(Un nouveau progrès de la chimiothérapie antituberculeuse). A. Ravina, Paris, France.* Presse méd. 57: 343-344, April 16, 1949.

Fifteen years ago there was consensus of opinion among all experts that no effective anti-tuberculous agent was available. Shortly after the introduction in 1935, by Domagk, of the sulfonamides, related compounds were tested for their activity against tubercle bacilli. The first such substance to be found possessing some activity was para-diaminophenylsulfone. It inhibited tubercle bacilli in vitro and to some extent in experimental animals.

A similar compound, promine, was tried with some success in man and soon other sulfones, particularly sulphetrone in England and promizole in the United States were investigated in human tuberculosis. The advent of streptomycin displaced attention from these compounds for at least two years. When it was discovered, however, that tubercle bacilli relatively quickly developed resistance to the new antibiotic, combinations of streptomycin with other drugs were thought of. Both para-amino salicylic acid and promizole were reinvestigated in this direction, and the former compound is of some promise in having bacteriostatic action against streptomycin-resistant tubercle bacilli.

In 1946 Domagk and his group announced that a new sulfone, thiosemicarbazone, showed activity against experimental tuberculosis. The results were promising enough to warrant trial in human cases of the disease. In February 1949 Heilmeyer published his first results obtained in patients with this drug. He stressed that the new drug had very little in vitro activity against the tubercle bacillus but that it was remarkably effective against exudative forms of tuberculosis.

The new drug effected apparent cure in 80% of cases of tuberculous laryngotracheitis, and was highly effective also in intestinal and lower urinary tract tuberculosis. It failed in most cases of tuberculous disease of the kidney. It was successful in many cases of early infiltrative pulmonary tuberculosis and tuberculous pleurisy. The daily doses have ranged from 0.25 to 1.0 Gm., but probably one tenth of that is effective. There have been occasional instances of gastrointestinal disturbance, anemia, proteinuria, and agranulocytosis with earlier preparations, but it is believed that the impurities responsible for these side effects can be eliminated.

Thus thiosemicarbarzone promises to be a useful addition to the steadily growing armamentarium of effective antituberculous agents. 12 references.

Combined Therapy by Streptomycin and Pneumothorax in Fibrocaseous Pulmonary Tuberculosis of the Adult. (*Streptomycine et pneumothorax associés dans le traitement précoce de la tuberculose pulmonaire fibro-Caséeuse de l'adulte.*) *Ch. Mattei, P. Balozet et C. Mattei, Marseilles, France.* Bull. Acad. nat. méd. 133: 22-23, Jan. 4, 1949.

Streptomycin therapy alone has given very encouraging results in a variety of forms of tuberculosis in the adult. However, recently even better results have been observed with a combination of intramuscular streptomycin administration and early pneumothorax, in fibrocaseous lesions with cavitation. The essential point of this combined therapy is the early institution of collapse.

In 6 cases which were observed for 6 to 10 months, the following regimen was instituted with good results: Treatment was begun by the daily intramuscular administration of 2 Gm. of streptomycin for 10 days to 2 weeks. There was prompt defervescence, slight weight gain, return of

appetite, marked subjective improvement and objective regression of the roentgen ray shadows. About the 15th day therapeutic pneumothorax was instituted. In 3 of the 6 cases pneumonolysis had to be performed because of massive adhesions. Subsequently the lung was collapsed satisfactorily in all patients. Neither pneumothorax nor pneumonolysis was accompanied by unfavorable reactions.

In all 6 patients progress was subsequently most gratifying with weight gains of 10 to 15 kg. in 4 months, in spite of poor conditions of hospitalization and general hygiene. A total of 250-300 Gm. of streptomycin was administered in an uninterrupted course, together with regular filling of the pneumothorax in this first phase of therapy. This part of treatment was carried out in a city hospital, without adequate general rest, care, or satisfactory environment. It was apparent that streptomycin had significant synergistic action with the collapse therapy that placed the lung at rest.

The second phase of treatment consisted of sanatorium care for these patients in a rural environment. Improvement continued even after pneumothorax and streptomycin had been discontinued. In this limited number of cases the definite impression was gained that the total period of hospitalization and care was greatly reduced by this two-stage regimen. The early and vigorous collapse therapy combined with drug treatment appeared to arrest progression of the disease and prepare the way for more rapid healing under sanatorial care.

It is proposed to extend this form of two-stage treatment to patients with other forms of tuberculosis in order to take advantage of the increased speed with which these patients may be returned to their homes and occupations. The social advantages of such regimes is discussed and the decreased cost to the state emphasized.

A Method of Desensitization Used to Avoid Sensitivity Reactions to Streptomycin. *(Méthode de desensibilisation contre les accidents de sensibilisation à la streptomycine.) Ch. Mattei and P. Balozet, Marseilles, France.* Bull. Acad. nat. méd. 133: 23-25, Jan. 4, 1949.

Sensitivity reactions to streptomycin occur not infrequently in the course of drug therapy of tuberculosis. Since it is often vitally important to continue the drug treatment in spite of such reactions, a method for desensitizing the patient has been devised and found successful in many patients.

Sensitivity reactions commonly are encountered about the 20th to 30th day of treatment, after 40 to 50 Gm. of streptomycin have been administered. In 30 per cent of all cases there is vertigo and nausea, either transient or progressive. About 1 in every 10 patients develops morbilliform eruptions with significant pruritus and fever. Local or generalized eczema may be seen, and occasionally a painful stomatitis interfering with food intake.

It is felt that sudden reactions encountered in the satisfactorily progressing cases of tuberculous meningitis may be on the basis of a sensitivity reaction. Very rarely, true anaphylactic shock may be encountered.

When the sensitivity reaction of significant severity is noted, streptomycin treatment should be stopped for 2 to 3 days, and then started again by the method indicated below. If the reaction is relatively mild, desensitization may be attempted without rest period. Whenever injections are started again minute amounts of streptomycin are used at first. It is suggested that two doses daily be given, first intracutaneously, later subcutaneously and intramuscularly, beginning with 1/20 mg. per injection and progressing to 340 mg. in 7 days, when the usual full dosage may be resumed. 1 reference.

Report on the First 100 Cases of Tuberculous Meningitis Treated with Streptomycin and Observed for 18 Months: Evaluation of Prognosis. (*Sur les 100 premiers cas de méningite tuberculeuse traités à la Clinique de la Tuberculose par la streptomycine. Résultats après un recul moyen de dix-huit mois. Les étapes du prognostic.*) *E. Bernard, B. Kreis, Mlle. Lotte, P. Chiche and P.-Y. Paley, Paris, France.* Bull. acad. nat. med. 133: 45-51, Jan. 11, 1949.

One hundred unselected cases of tuberculous meningitis were treated with intramuscular and intrathecal streptomycin. All but 2 were adults. The average period of observation since the beginning of therapy was 18 months. In 87 patients, including all survivors, tubercle bacilli were recovered from the cerebrospinal fluid, proving the diagnosis. In the others, no complete bacteriological proof was established because the patients died too soon.

Of the 100 treated patients, 23 were still alive at the end of 18 months. Twenty appeared to be cured, and had returned home to their normal life, while 2 had some neurological sequelae or intellectual impairment, and one had continuing evidence of meningitis.

Among the 77 fatalities, 18 died within 5 days after treatment was started. Many among them were in extremely poor condition on arrival in the hospital, often having been transported long distances. Twenty-six others died within the first 3 months of therapy, 23 between the 3rd and the 6th months of therapy or observation, and 10 died after the 6th month of observation.

Total length of therapy was very clearly related to the number of relapses and deaths in any given group. Of 7 patients treated 3 months or less, all relapsed and died. Of 11 treated between 3 and 7 months, 4 survived, and of 11 patients treated 7 to 11 months, 10 survived. The obvious conclusion must be drawn that for best results tuberculous meningitis should be treated with streptomycin 9 months or longer.

In the relapses occurring after voluntary arrest of treatment, tubercle bacilli were uniformly recovered from the spinal fluid. These organisms, however, were largely still sensitive to streptomycin in the test tube. Retreatment of 15 such cases resulted in the cure of 5. Among 8 persons who experienced marked improvement and apparent cure followed by relapse during drug therapy, only 1 ultimately survived.

It is emphasized that patients were accepted on the basis of diagnosis only, without any attempt at selecting suitable cases. The large number dying within just a few days after being brought to the hospital make it clear that the first prerequisite for good prognosis must be early and adequate treatment. It is furthermore stressed that clinical relapse is preceded by a long interval of recurring abnormalities of the spinal fluid. It is therefore essential that all patients under observation not only be watched clinically but also have regular examination of their spinal fluid, even when completely asymptomatic.

Intrathecal streptomycin is considered an essential part of therapy not only during the first few weeks or months, but during most of the period of drug treatment. A plea is made to have the spinal fluid of all persons with active pulmonary tuberculosis examined to find early evidence of meningeal involvement and make it accessible to treatment.

In another series of 93 children (part of a larger series under study), observed by Dr. Robert Debré at *l'hospital des Enfants-Malades*, 63 died and 30 survived. Of those who died, 28 succumbed within 1 month of entering the hospital; the others in periods ranging from 1 to 16 months. Of the 30 survivors, 23 appeared well at the end of 16 months, while in 7 others treatment with streptomycin continued. 3 tables.

Clinical Evaluation of a New Sulfonamide—Gantrisan. *Paul S. Rhoads, Floyd A. Svec and Joseph H. Rohr, Northwestern University Medical School, Chicago, Ill.* Quart. Bull Northwestern Univ. M. School 23: 104-11, Spring 1949.

Recently a new sulfa compound, 3,4—dimethyl—5—sulfanilamidoisoxazole, was synthesized by Hoffman - La Roche, Inc. The clinical advantage claimed for this compound was its high solubility and antibacterial effectiveness against the gram positive organisms as well as many of the gram negative bacteria.

Preliminary studies of the drug indicated that it had a high solubility between pH 5.5 - 6.5. The in vitro bacteriostatic effect was found to be about the same as sulfadiazine against the gram positive organisms tested *(Streptococcus viridans, S. faecalis, S. hemolyticus, Staphylococcus aureus, and the pneumococcus)* and was very effective against *E. coli.*

NU 445 or Gantrisan was administered to 91 patients for a variety of conditions with a clinical response which compared favorably with other sulfonamides. Included in the series of patients treated were 7 cases of meningococcal meningitis that showed complete recovery; 29 urinary tract infections, 15 of which showed complete recovery and 11 that showed incomplete bacteriostasis; and 10 cases of upper respiratory infections with a favorable response in 7. There were also 3 cases of erysipelas and 1 of scarlet fever with recovery, as well as 2 cases of cellulitis.

The drug was administered in average doses of 6 Gm. per day, 1 Gm. every 4 hours. It was supplied in ampule form as well as oral tablets. It could be given with intravenous saline or glucose, directly into the vein, or intramuscularly. The average blood level on a 6 Gm. dose was 9.17 mg.% when given orally, 16.7 mg.% when given intravenously and 9.29 mg.% when given intramuscularly. Spinal fluid levels were found to be between 1/2 and 1/3 of simultaneously drawn blood levels. Excretion studies indicate that 80-90% of a single dose can be recovered in the urine in 48 hours and about 50% of this is excreted during the first 8 hours.

In the series of 91 treated cases, nausea occurred in 5, vomiting in 2, headache in 1, and a generalized skin eruption in 1 patient that had been sensitized previously to other sulfas. Crystals thought to be Gantrisan was found in the urine of 2 patients but then cleared while the drug was continued. No instances of renal complication were encountered, even though no alkali therapy was used. 9 references. 6 tables. 2 figures.—*Author's abstract.*

Aureomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease). *Fordyce R. Heilman, Mayo Clinic, Rochester, Minnesota.* Proc. Staff Meet. Mayo Clin. 23: 569-73, Dec. 8, 1948.

Mice were infected with a strain of relapsing fever spirochetes, *Borrelia novyi*, and treated with various doses of aureomycin. When mice with established infections were treated with three subcutaneous injections per day for three days, the daily dose containing 0.18 mg., the blood was cleared of spirochetes within 24 hours and there were no relapses. Two doses given orally 6 hours apart, and containing a total of 1 mg. of the drug, also were effective.

Comparison of these results with those obtained in previous experiments with penicillin indicate that on the basis of weight, aureomycin is approximately three times as active as crystalline penicillin in the treatment of this type of experimental infection.

Syrian hamsters were infected with lethal doses of *Leptospira icterohaemorrhagiae* and treated with two subcutaneous injections of aureomycin per day. Treatment was started 21 hours after infection, and was continued for 10 days. Total daily doses of 0.125 mg. gave complete protection.

Comparison of these results with those secured in previous studies with penicillin in the treatment of this type of experimental infection indicate that on a weight basis aureomycin is at least twice as effective as crystalline penicillin. 8 references.—*Author's abstract.*

Aureomycin in the Treatment of Primary Atypical Pneumonia. *Maxwell Finland, Harvey Shields Collins, and Edward Buist Wells, Harvard Medical* School, Boston City Hospital, Boston, Mass. New England J. Med. 240: 241-46, Feb. 17, 1949.

The activity of aureomycin against infections with all the known rickettsias and the viruses of the psittacosis-lymphogranuloma venereum group (all of which may produce human infection virtually indistinguishable

from primary atypical pneumonia) made reasonable the attempt to determine empirically whether aureomycin would favorably influence the course of primary atypical pneumonia in which the etiologic role of any known agents can be ruled out.

The patients who were treated were all acutely ill and febrile when aureomycin was started. Patients were not treated when there was any reason to suspect that the acute disease was receding, as evidenced by recent improvement in the general appearance of the patient or in the fever or symptoms, after a brief period of observation if necessary. Each patient had a history consistent with primary atypical pneumonia and also physical, laboratory and x-ray findings characteristic of the disease. In each case, significant titers of cold agglutinins were present in the blood at the appropriate time.

The first 20 consecutive patients who satisfied these criteria were all markedly improved clinically and were afebrile within 12 to 48 hours (the great majority within 24 hours) after the first dose of aureomycin was given. The pulmonary lesions cleared rapidly in every case. The findings suggested that aureomycin had a favorable effect on the course of the disease.

The difficulties in evaluating the results of therapy in primary atypical pneumonia were discussed in relation to the natural course of the disease. 10 references. 3 figures.—*H. S. Collins.*

Abuses and Dangers of Local Sulfonamide Therapy. *(Les abus et les dangers de la sulfamidothérapie locale). C. Garnier, Paris, France.* Presse méd. 56: 850-51, Dec. 4, 1948.

In the last few years the use of sulfonamides in the form of powders, salves, lotions, nose drops, etc. has reached unbelievable proportions. The many preparations applicable to the skin or mucous membranes are among the commonest medicaments used by the practitioner . In addition, these remedies are now found in many households and are used quite indiscriminately by the laity. This practice must be condemned, since it is often not only useless but harmful.

The main side effects of local sulfonamide therapy are local reactions, general cutaneous eruptions, and systemic reactions of hypersensitivity. The local reactions commonly occur after prolonged use of the local preparation but sometimes after only two or three days. They usually appear in the form of erythema, pruritus, vesication and oozing of serous fluid. The reaction is essentially a contact dermatitis, and it aggravates the underlying lesion seriously. If the nature of the process is not recognized promptly and sulfonamide medication is continued, the reaction tends to spread and subside only after a long time.

General cutaneous eruptions may be scarlatiniform and independent of exposure to light or they may be limited to uncovered portions of the body, particularly the face, forearms, hands, neck, etc. The etiology of the eruption is usually not apparent to the patient, and when faced with such a clinical picture one has to question the subject carefully about the use of sulfonamdies systemically or locally alike. Eruptions of a general nature may be uticarial, scarlatiniform, papular, exzematous, etc. Systemic evidence of sensitization may appear in the form of hematuria, proteinuria, arteritis and others. The indiscriminate local use of sulfonamides is therefore to be condemned.

Effect of Para-Aminobenzoic Acid on Murine Typhus. A Clinical Study of 60 Cases. *R. S. Diaz-Rivera, C. Guzman Acosta, Pedro J. Collazo and A. Pomales Lebron, Ph.D., San Juan, Puerto Rico.* Am. J. M. Sc. 217: 13-20, Jan. 1949.

The authors studied 60 proven cases of murine (endemic) typhus, 33 of whom received para-aminobenzoic acid, 4 Gm. as an initial dose, and then 2 Gm. every 2 hours, in tablet form, until the temperature was normal and the patients had entered the stage of convalescence. The clinical course was compared with that of 27 untreated cases that served as controls. The two series were almost identical as regards sex, age, and race.

A secondary rise in temperature after lysis was observed in 78% of the untreated and in 30.3% of the treated cases. The duration of fever before admission averaged 6.2 days for the control series. Treatment was started between the first and twelfth day, with an average of 6.5 days, in those that received para-aminobenzoic acid. The duration of illness after hospitalization for the untreated group averaged 8.8 days, while in the treated it was only 2.2 days. The total duration of the disease in the treated group averaged 8.7 days, as compared with 15 days among the controls. The total amount of the drug administered averaged 121.4 Gm. received in 1.8 to 9 days and ranged from 44 to 219 Gm.

Improvement in the headache, bodyaches, prostration, constipation and photophobia was observed in the majority of patients within 48 hours after the initiation of therapy. The drug, however, failed to prevent the appearance of the rash, or to alter its distribution, in 12 of the cases. The rash appeared during treatment in 5 cases, and in 7 after the temperature had become normal. Treatment was started early in the course of the disease in all of these cases. On receiving treatment, when present previous to the onset of therapy, the rash assumed a violaceous color and tended to disappear more rapidly than in the control group.

In general, the patients receiving treatment early in the course of the disease responded better than did those in whom therapy was delayed for more than a week, but it was noted that in 6 patients administration of the drug was started after the seventh day of illness, and yet the results were

favorable. This seems to indicate that although favorable results may be obtained in the treatment of endemic typhus after the seventh day of illness, the greater efficacy of early therapy should be emphasized.

There were no toxic symptoms attributable to para-aminobenzoic acid. From observations in 6 patients of the control series, it appeared that penicillin in doses of 20,000 units given intramuscularly, every 3 hours, fails to alter the course of murine typhus in man. Sulfadiazine, administered in proper doses to 9 patients for a period which averaged 3.5 days resulted in no toxic or beneficial effects. From the study of 19 cases of diseases other than an endemic typhus (typhoid fever, influenza, pneumonia, malaria) it appeared that para-aminobenzoic acid does not exert a beneficial effect on their clinical course.

The fact that 5 of the treated patients developed the rash during the course of therapy and 7 others after the disappearance of the fever, and after convalescence had seemingly started, made the authors speculate on the mode of action of para-aminobenzoic acid and on the pathogenesis and immunology of the disease. These observations suggested that the drug fails to interfere with the pathologic alterations in the vascular system of the diseased, and that once the rickettsiae are fixed in the tissues their destructive action continues for a time in spite of the drug. The rapid favorable response observed in some cases may indicate an attenuation of the toxemia produced by the rickettsiae, the drug being suppressive but not curative. It is suggested that para-aminobenzoic acid acts as any other antibiotic, inhibiting the growth of the organisms, probably in an indirect manner. The authors compared the action of the drug in murine typhus with that of penicillin in pneumonia. The latter promptly reduces the toxic manifestations of the disease, while the pathologic process continues its natural, though perhaps abbreviated course. It is possible that para-aminobenzoic acid attenuates the rickettsiae but does not kill the organisms outright, allowing the host's natural defensive mechanisms to eradicate the infection through the establishment of immunity. That the final disposal of the rickettsiae is a function of the host, and that it is aided only in part by the drug, is evidenced by the secondary rises in temperature observed among the great majority of the untreated, and in some of the treated patients. Such rises in temperature probably represent minor recrudescences of the disease at a time when immunity is not yet solidly established. This is substantiated by the reappearance of the original symptoms of typhus with the secondary rise in temperature.

The authors call attention to the possibility that the rickettsiae of murine typhus are not completely destroyed by the body, and that the disease may behave like epidemic typhus in which a delayed recrudescence, as exemplified by Brill's disease, may occur. Perhaps the organisms remain in a dormant state and minor febrile illnesses which pass undiagnosed may be recurrences of the disease.

This study shows that heavy doses of para-aminobenzoic acid are safe and beneficial in the management of murine typhus, especially when treatment is started early in the course of the disease. 18 references. 3 tables.—*Author's abstract.*

(Although serious toxic reactions to para-aminobenzoic acid are uncommon, a significant number have been observed. Aureomycin appears to be safer and more effective than para-aminobenzoic acid in the treatment of rickettsial infections.—ED.*)*

Volatile Antibiotics: Beta-antibiotics. *(Antibiotiques volatils: Beta-antibiotiques). M. W. N. Markoff, Institute of Microbiology, School of Medicine, Sofia, Bulgaria.* Presse méd. 56: 901, Dec. 25, 1948.

The antibacterial properties of the well established antibiotic agents manifest themselves only on contact with the microorganisms. The substances described here are volatile and consequently reach the bacteria in the gaseous state.

It was observed that a species of Penicillium isolated from wine, when grown on solid media, developed a peculiar aromatic odor after 4 to 5 days of incubation. The odor appeared to be associated with the appearance of reddish droplets on the aerial growth of the organism. Later in the growth of the organism the droplets were no longer formed, but the aromatic odor persisted for about four weeks. This period coincided with the presence of volatile antibacterial substances. It was observed that cultures of this species of Penicillium grown in special flasks gave off significant amounts of volatile substances which could be conducted through a series of tubes toward the surface of agar plates inoculated with a variety of bacteria. Most of such gram-positive bacteria were strongly inhibited while most gram-negative bacteria remained unaffected. The maximum production of these volatile substances, called beta-antibiotics, took place about the fifteenth day of incubation, while small amounts of alpha-antibiotics (penicillin) were produced chiefly from then on.

Differential test indicated that actually the very first portion of aromatic volatile substance given off by this Penicillium only had feeble antibacterial activity and consequently that odor was only coincidental with antibacterial activity. It was likewise established that significant amounts of alcohol, acetone or other metabolites produced by the organism had no antibacterial effects on the test organisms and that these substances were not responsible for the beta antibiotic effect observed.

Apart from the Penicillium species described, other organisms were found to produce beta-antibiotics of similar effects. Among them were actinomycetes and a number of gram-negative bacteria like Proteus, Pyocyaneus and some dysentery bacteria. The beta antibiotics elaborated by all these organisms exerted their action only on gram-positive bacteria, and appeared to be bactericidal. These investigations are in progress.

The Treatment of Typhoid Carriers with Penicillin and Sulphathiazole. *Joseph W. Bigger and R. A. Daly, M.Sc., The University of Dublin, Dublin, Ireland.* Lancet 1: 296-99, Feb. 19, 1949.

Ten chronic typhoid carriers were treated with 8 Gm. sulphathiazole and 4.8 million units of penicillin daily for 6.5 days. Only one of the ten was cured. Three of the carriers in whom the treatment had been unsuccessful were retreated as before for four periods each of three days with intermissions of 2, 3, and 4 days between the periods. The total medication over 21 days was 100 Gm. sulphathiazole and 57.6 million units of penicillin. Two of these three carriers were cured. The criterion of cure relied upon was failure to isolate *S. typhi* from feces or urine, using Wilson and Blair's medium and tetrathionate broth. Specimens were cultured daily for 10 days, on alternate days for 10 days, once a week for 6 weeks, once a month for 9 months and, about one year after the termination of treatment, daily for 5 days.

In the case of the three cured carriers, 35 specimens of feces and urine were examined according to this schedule, all with negative results. The last specimens were examined 384 days (1 case) or 346 days (2 cases) after the termination of treatment. It is claimed that this intermittent method of treatment of the carrier condition with sulphathiazole and penicillin is the most successful yet described and that, with minor modifications, a still higher proportion of carriers could be cured. 6 references. 2 tables.—*J. W. Bigger.*

3. Diseases Caused by Animal Parasites

Pneumococcal Pneumonia Treated with Aqueous Penicillin at Twelve-Hour Intervals. *Philip A. Tumulty and Gordon Zubrod, Johns Hopkins University School of Medicine, Baltimore, Md.* New England J. Med. 239: 1033-36, Dec. 30, 1948.

Although the efficacy of penicillin therapy of pneumococcal lobar pneumonia is well established, the manner in which it may be employed to give the best therapeutic results with the least discomfort to patients is still debated. Penicillin has generally been administered either in aqueous solution at frequent intervals or in some repository form because of the assumption that it is necessary to maintain constantly a greater concentration of penicillin in the blood than suffices to inhibit the particular organism if therapy is to be effective. There is both experimental and clinical evidence that this assumption is not valid.

This study was carried out to determine how successfully pneumococcal lobar pneumonia could be treated with aqueous crystalline penicillin G given at 12 hour intervals. A consecutive series of 79 patients having clear-cut pneumococcal lobar pneumonia was treated with aqueous crystalline penicillin G given intramuscularly at 12 hour intervals. Three hundred thousand units of a potassium salt of crystalline penicillin G were given initially and repeated at 12 hour intervals until the temperature remained normal for 24

hours, when 300,000 units were given at 24 hour intervals for an additional 48 hours, unless there was some indication for more prolonged therapy. The therapeutic response of this group was contrasted with that observed in 69 patients who received aqueous penicillin intramuscularly every three hours and 58 patients who were given 300,000 units of penicillin in oil and beeswax every 24 hours. Only cases of clear-cut pneumococcal lobar pneumonia were included, selection being based upon a characteristic history, physical and x-ray evidence of pulmonary consolidation, fever, leukocytosis and the presence of typable pneumococci in the sputum, nasopharynx or blood.

In general, the pneumonia in the three groups studied was considered to be of average and equal severity. Within the limitations of this type of clinical study there was no superiority in the response of patients receiving frequent doses of aqueous penicillin or repository penicillin to the response of those receiving aqueous crystalline penicillin G at 12 hour intervals. What minor differences there were favored the latter schedule. Death and complications each occurred in but 2.4% of the group given discontinuous therapy. In terms of the number of febrile days, the number of days in bed and the period of hospitalization, administration of penicillin at 12 hour intervals was at least as effective as the schedules designed to maintain a constant penicillin blood concentration.

Since the therapeutic response was so satisfactory it appears questionable whether a constant blood level of penicillin is necessary in the treatment of pneumococcal lobar pneumonia. Consequently, the employment of repository forms such as penicillin in oil and beeswax or procaine penicillin or the administration of aqueous penicillin at shorter intervals is thought to be unnecessary in the therapy of lobar pneumonia. Whether infrequent administration of penicillin in aqueous solution would be effective in the treatment of other infections can be established only after careful clinical observation. Attention is called to the value of a large initial "priming" dose of penicillin in the treatment of individuals with severe infections. 14 references. 2 tables.—*Author's abstract.*

Treatment of Pneumonia with Intramuscular Aqueous Penicillin Once a Day. *William Weiss and Israel Steinberg, Sydenham Hospital, New York, N. Y.* Am. J. M. Sc. 217: 86-91, Jan. 1949.

Since several recent articles have appeared in the literature to suggest that infrequent large parenteral doses of aqueous penicillin are as effective as frequent small doses in the treatment of both experimental and clinical infections, it was decided to determine the effectiveness of treating pneumonia in man with 300,000 units of aqueous penicillin G intramuscularly once a day. This form of management was carried out in 30 consecutive cases admitted to a general hospital, the daily injections being continued until the temperature of the patient was normal for three days.

The patient material was varied. There were 15 males and 15 females ranging in age from 16 to 72 years, and the degree of illness was mild in 8

cases, moderate in 14 cases and severe in 8 cases. The pneumonic process was lobar in all but 2 cases, and involved more than one lobe in 3 cases. Sputum studies in 28 patients showed the presence of the pneumococcus in 26, sometimes associated with other bacteria. Blood culture on admission was positive for pneumococcus in just one case. Sixty per cent of the patients responded with a crisis within 12 to 36 hours after the first injection. Thirty per cent responded with lysis. One case, complicated by glomerulo-nephritis, was classified as a failure, although her pneumonia resolved in the usual time, because no definite response to the antibiotic could be detected. There were 2 deaths (6.6%); one was complicated by acute alcoholic delirium and showed an enlarged fatty liver at necropsy, while the other death was due to acute pulmonary edema in a 72 year old female with hypertensive heart disease demonstrated at necropsy. It was of particular interest that post-mortem cultures from the pneumonic lung tissue were sterile in both of these cases.

Complications of the pneumonic process consisted of pleural effusion in 2 cases (6.6%) and delayed resolution in 3 patients (10%); one of the latter was shown to have an underlying bronchiectasis by bronchogram. One patient who responded to 4 injections with an immediate crisis had a second attack in another lobe after the first lobe had cleared roentgenographically, and again responded to the same treatment in the same manner but was given 5 injections the second time. One severely ill patient who responded with lysis showed a cavitation which disappeared roentgenographically as her pneumonia resolved.

The results in this series were approximately the same as those which have been reported in the literature following the administration of aqueous penicillin at shorter intervals. Therefore the therapeutic effect of penicillin is not dependent on the continuous maintenance of a penicillin level in the blood stream but rather on the persistence of penicillin effect in the infected tissues of the host. 18 references. 2 tables.—*William Weiss.*

(See also *Quarterly Review of Medicine*, 6: 97, May, 1949).

Treatment of Pneumonia by Single Injection Daily of Potassium Penicillin in Beeswax Peanut Oil Mixture. *Italo F. Violini, Wm. S. Hoffman and James J. Hughes, Hektoen Institute for Medical Research of Cook County Hospital and Loyola University School of Medicine, Chicago, Ill.* Illinois M. J. 95: 147-55, March 1949.

A series of 104 unselected patients with lobar pneumonia were classified according to the organism causing their infection. The majority were seriously ill. Patients over 50 years formed 29.8 per cent of the total; 32.7 per cent had cardiovascularrenal or other complications and 62 per cent had the more virulent type of pneumococcic pneumonias.

All the patients were treated with a sterile suspension of potassium penicillin G in peanut oil containing 4.8% by volume of beeswax. Potassium penicillin G was used because its high potency of 1,435 Oxford units per mg.

permitted the full daily dose of 300,000 units to be contained in 1 cc. of the mixture. The entire daily dose was given in a single intramuscular injection over the insertion of the deltoid muscle or in the side of the thigh over the fascia lata. The heating technic of Code and associates was used to facilitate withdrawal of the mixture from the container. Treatment was continued until 72 hours after the febrile period, but no other specific therapy given. Penicillin concentration levels in plasma were determined in 88 patients of the series. Only 6.6% of the cases show less than 0.03 and 0.01 units per cubic centimeter of plasma 24 hours after injection. This concentration still had some therapeutic value because it corresponds to the minimum amount of penicillin to which pneumococci are sensitive. The goemetric average of penicillin concentrations at the 24 hour interval was 0.10 units, considerably more than necessary.

There was good clinical response, the temperatures of 24% of the patients returning to normal within 24 hours and 61.5% within 72 hours. The mortality rate was 3.8%. This was not considered significant because serious concurrent disease or complications were present with each fatality, so that it was uncertain whether or not pneumonia was the primary cause of death. Toxic reactions were negligible.

Disadvantages of this method are the expense and the amount of local inflammatory reaction at the site of injection. Advantages are that serious toxic reactions are eliminated and frequent disturbance of the patient avoided. Failure to respond to this treatment after 72 hours requires revaluation of the patient. 21 references. 10 tables.

A New Method of Maintaining Therapeutic Penicillin Blood Levels on Oral Administration. *George Cronheim and Mary E. Baird, Bristol, Tenn.* Journal Lancet 69: 56-59, Feb. 1949.

Penicillin has been administered orally, dissolved in an aqueous suspension of sulfadiazine and sulfathiazole together with sodium citrate and sodium lactate as systemic alkalizers. The sulfonamide preparation had the following composition: sulfadiazine, 5%; sulfathiazole, 5%; sodium citrate, 10%; and sodium lactate, 12%.

Fifty-one healthy adults, mostly males, took one single 10 cc. dose of the sulfonamide preparation, plus penicillin (50,000 to 300,000 units per dose) followed by 100 to 150 cc. of water. One blood sample was taken from each subject after a few hours. The penicillin serum levels were assayed by the method of Fleming et al (1947). The presence of sulfonamides in the serum of these subjects was not found to interfere with the penicillin determination.

Small doses of penicillin gave a relatively higher blood level than larger doses, indicating better utilization of small doses. The protective action of the sulfonamide preparation was such that even four hours after one oral dose of 50,000 units, the penicillin blood level was still about 0.03 units per cc. The time of giving the drugs in relation to food intake did not

influence the results. The possibility of a renal blockade was excluded as an explanation of the high penicillin blood level of 0.03 units per cc. For therapeutic use a dosage of 100,000 units of penicillin in 10 cc. of the sulfonamide preparation is recommended, after an initial dose of from two to three times this amount. The drugs should be given on a fasting stomach or between meals.

The alkali salts used, because of their buffering power, prevent destruction of penicillin by gastric juice. These salts may also favor absorption by an action on the pH of the stomach contents. 15 references. 4 tables.

The Oral Administration of Aureomycin (Duomycin) and Its Effect on Treponema Pallidum in Man. *Paul A. O'Leary, Robert R. Kierland and Wallace E. Herrell, Mayo Clinic, Rochester, Minn.* Proc. Staff Meet. Mayo Clin. 23: 574-78, Dec. 8, 1948.

Aureomycin is active against a number of organisms and has showed promise in the treatment of a variety of infections. The interest of the authors in the effects of aureomycin on syphilis was prompted by the work of Heilman who showed that aureomycin, weight for weight, is two to three times as effective as penicillin in experimental spirochetal infections. Two patients with primary lesions of syphilis have been treated with oral aureomycin. The first was a white man 38 years of age, who came to the clinic for examination because of a painless ulcer on the anterior surface of the scrotum of two months' duration. In the previous week an eruption of the lower lip, left axilla, palms and soles had developed and this was associated with malaise, sore throat and headache. Examination revealed a large superficial ulceration measuring 4 cm. in diameter on the anterior surface of the scrotum, the base and periphery of the ulcer being indurated. In addition, secondary lesions of syphilis were manifested; generalized maculopapular eruption, moist papules and mucous patches. The examination otherwise was noncontributory. Dark field examination of material from the scrotal ulcer revealed the presence of *Treponema pallidum*. The patient was hospitalized the same day and started on oral aureomycin (Duomycin) at 8 p.m.; 400 mg. was given every four hours. The dose of aureomycin was increased to 500 mg. every four hours on the fourth hospital day. The patient received 750 mg. every four hours from the sixth through the seventh hospital day and from then on he received 500 mg. every four hours throughout the rest of his hospitalization. The aureomycin given totaled 44.2 Gm. A febrile Herxheimer reaction was noted twenty-four hours after treatment with aureomycin was started. The results of the dark field examination were negative sixty hours after aureomycin treatment was begun and remained negative. Twelve hours earlier, there were but 1 or 2 sluggish *Treponema pallida* per microscopic field. The roseola was still present but the ulcer had begun to heal. In ninety-six hours the roseola had faded and the mucous patches had healed while the scrotal ulcer was rapidly healing. At the time of dismissal, sixteen days after admission, all lesions had healed but there was residual

induration at the site of the chancre. Prior to treatment, serologic reactions for syphilis were strongly positive and the titer was 256 Kahn units. Forty days after the onset of treatment, the titer was 32 Kahn units. Blood levels of aureomycin were checked at frequent intervals during therapy and varied between 2 and 4 micrograms per c.c. of blood while the patient was receiving 400 and 500 mg. doses of aureomycin but when the aureomycin was given in doses of 750 mg. every four hours the blood level was 8 micrograms per cubic centimeter.

The second patient, a white man aged 24, was seen because of a penile lesion of one week's duration. The ulcer measured 1 cm. in diameter and was located on the anterior surface of the penile shaft. There was peripheral induration of the lesion. There was no roseola or other objective evidence of syphilis. The results of dark field examination for *Treponema pallidum* were positive and on serologic examination for syphilis, negative Kline, Kahn and Kolmer reactions but a positive Hinton reaction were obtained. Aureomycin (Duomycin) was administered orally 750 mg. every four hours for fifteen days for a total dose of 67.5 Gm. Twelve hours after beginning treatment the results of dark-field examination for *Treponema pallidum* were positive, but at sixteen hours and thereafter they were negative. Four days after the beginning of treatment the primary lesion was 50% smaller. At the end of the treatment period the primary lesion was completely healed. Blood levels for aureomycin varied between 2 and 4 micrograms per cubic centimeter. The only objective evidences of untoward reactions were nausea, anorexia and, on one occasion, vomiting. At the end of the treatment there were mild perleche and a smooth reddened tongue indicating beginning vitamin B deficiency. Pretreatment serologic tests for syphilis were entirely negative, but eight days after the onset of treatment the serologic reactions had become positive and the quantitative Kahn units measured 8. Fourteen days after treatment was started there had been a reduction in the titer to 3 units and on the twenty-third day the reaction was negative. The untoward reactions noted to date have been those referable to the gastrointestinal system and manifested by nausea, anorexia and occasional vomiting. Stool specimens are rendered sterile by means of this drug and for this reason avitaminosis may develop. It is suggested then that vitamin supplements be given during the therapeutic period.

In conclusion, aureomycin appears to have definite antispirochetal activity when administered by the oral route. 7 references. 2 figures.—*Author's abstract.*

Paludrine in Malaria. *Philip Manson-Bahr, Hospital for Tropical Diseases, London, England.* South African M. J. 22: 804-805, Dec. 25, 1948.

Paludrine exerts an action somewhat different from that of quinine or atabrine on malaria plasmodia. Its effect upon *Plasmodium vivax* and *P. falciparum* is only equalled by plasmoquine, but it is more efficient and less toxic than that drug. Its action upon subtertian malaria is as satisfactory

but neither as rapid nor as effective as atabrine. Nor does it eliminate *P. vivax* from the circulation any better than quinine, although single 100 mg. doses suppress individual attacks. Paludrine has absolutely no toxic properties and is tolerated in larger doses than those necessary to eradicate the malaria parasite. It is effective against all species but especially *P. falciparum*. Its chief value is as a prophylactic. It acts as a schizonticide and most effectively on the early asexual forms by interfering with nuclear division but does not eradicate gametocytes more quickly than quinine or atabrine. It has been proved that mosquito gut infection is completely sterilized in one or two hours after a carrier has received 150 mg. of paludrine.

Therapeutic doses have varied from 5 mg. twice daily to 750 mg. Severe cases may also be given 5 mg. intravenously. The best dosage for *P. falciparum* (subtertian) infections is 100 mg. three times daily for 7 to 10 days, though it is claimed that an attack can be suppressed by a single dose of 25 mg. *P. vivax* (benign tertian) and *P. malariae* (quartan) infections require as much as 250 mg. three times daily for the same period. It has been demonstrated, however, that relapses are not prevented by daily doses of 500 mg. paludrine for 10 days and that more relapses occur than on a similar course of quinine-plasmochine. Furthermore, chicks infected with *P. gallinaceum* have been found to develop resistance to paludrine from sub-therapeutic doses and this property is transmitted by mosquito passage.

Paludrine is apparently the ideal casual prophylactic, preventing human infection through its action upon the sporozoites or intermediate malarial parasite stages in the body. It does not prevent sporozoites from penetrating the skin but destroys the exoerythrocytic forms of the parasites. Prophylactic dosage is 0.1 Gm. daily for 10 days. The same dose once or twice weekly is also an effective suppressive agent but, as before stated, is more effective against subtertian than the benign tertian form. Prospective travellers in malarial areas should, therefore, take 0.1 Gm. paludrine for at least 10 days previously. 10 references.

Resistance to Proguanil (Paludrine) in a Mammalian Malaria Parasite *(Plasmodium Cynomolgi). Frank Hawking and W. L. M. Perry, National Institute for Medical Research, London, England.* Lancet 2: 850, Nov. 27, 1948.

A strain of monkey malaria, *Plasmodium cynomolgi*, has been subjected to repeated sub-effective treatment with paludrine. Initially two daily doses of 0.03 mg. per Kg. made the blood free from parasites. After 14 months the resistance to paludrine has increased about 1,000 times, and doses of 25 to 30 mg. per Kg. now fail to abolish the blood parasitemia in four treated monkeys. These doses are approaching the maximum tolerated dose in monkeys.

In view of the close similarity between *P. cynomolgi* and *P. vivax*, it seems probable that benign tertian malaria in man might become resistant to paludrine, but this process will probably take a long time to complete, even under favorable conditions. 2 references.—*W. L. M. Perry.*

"Paludrine" (Proguanil) in Prophylaxis and Treatment of Malarial Infections Caused by a West African Strain of *P. Falciparum*. *G. Covell, W. D. Nicol, P. G. Shute and M. Maryon, Horton Hospital, Epsom, Surrey, England.* Brit. M. J. 4593: 88-91, Jan. 15, 1949.

A series of prophylactic and therapeutic trials with proguanil was carried out at Horton Hospital, Epsom, against a strain of *Plasmodium falciparum* obtained from a native of Lagos, Nigeria, West Africa. The drug acted as a casual prophylactic of infections with this strain of parasite. The prophylactic dosage recommended for non-immune adults in West Africa is 100 mg. daily. Proguanil controlled the clinical attack caused by infections with this strain, but its action was somewhat less rapid than that of mepacrine or quinine. It failed to effect radical cure when given alone.

Radical cure was effected with (a) 300 mg. proguanil twice daily for 10 days reinforced with 900 mg. mepacrine given in 3 doses on the first day of treatment (6 cases); (b) 300 mg. proguanil twice daily for 10 days reinforced with 30 gr. quinine hydrochloride given in 3 doses on the first day of treatment (5 cases); and (c) 10 gr. quinine hydrochloride twice daily for 10 days (5 cases).

Following a course of 300 mg. proguanil twice daily for 10 days, gametocytes were rendered non-infective to mosquitoes as long as they continued in the peripheral blood in sufficient numbers for infection to occur. Reinforcement of a course of 300 mg. proguanil twice daily for 10 days with 900 mg. mepacrine given in 3 doses on the first day of treatment shortened the average duration of pyrexia and clinical symptoms by approximately twenty-four hours.

It is considered that such a course, followed by a maintenance dose of 100 mg. proguanil daily for the ensuing six weeks, would fulfill the main objectives in the treatment of *P. falciparum* malaria infections, namely, rapid termination of the clinical attack, a high radical cure rate, sterilization of gametocytes and minimum risk of injurious side-effects. 7 references. 3 tables.—*Author's abstract.*

Evaluation of the Complement Fixation Test for Malaria. *A. D. Harris (Sr. Serologist, U. S. P. H. S.) and L. M. Reidel (Asst. Serologist, U. S. P. H. S.).* Am. J. Trop. Med. 28: 787-95, Nov. 1948.

The Kolmer complement fixation test for malaria was resurveyed to determine its value as an accurate method of identifying infected persons in an endemic area. Antigens prepared from dehydrated corpuscle masses

obtained from infected monkeys (knowlesi) or chickens (gallinaceum) were used. Gallinaceum antigens were prepared by titration and dilution and the knowlesi antigen by extraction with buffered saline.

The chief difficulty in stabilizing the level of reactivity in the complement fixation test was the marked variability of the malaria antigens used. Antigen is a chief determinant of reactivity, so that an adequate supply of constant quality is of paramount importance for complement fixation tests. Recorded findings on specimens from normal donors showed less than 1% of false positive reactions for malaria. Serum from tubercular patients gave similar reactions, but serums from syphilitic donors gave more positive malaria reactions. Positive syphilitic reactions are difficult to differentiate from positive malaria reactions in nonsyphilitics. This militates against the use of this type of testing for random surveys, as the value of positive malaria reactions would be greatly reduced in populations having moderate to considerable syphilis. The highest titered reactions in the malaria complement fixation tests were obtained during or after recorded parasite counts, indicating that most positive serologic findings on random blood specimens in field surveys might be expected soon after the period of maximum parasite count. More positive reactions were obtained in this study with the most reactive gallinaceum antigen than with the knowlesi antigens used. Positive findings were sometimes obtained with the knowlesi antigens from serums that reacted negatively with gallinaceum antigen. Both types of antigens should be used for a test of maximum sensitivity, because more positively reacting serums were found in that way than with either antigen alone. 8 references, 7 tables.

Transient Urticaria in Malaria. *Milton Kissin and Ralph J. Adleman, Beth Israel Hospital, New York, N. Y.* Am. J. Trop. Med. 28: 797-802, Nov. 1948.

Transient urticaria is sometimes a helpful diagnostic feature in malaria. Literature on the subject is reviewed and observations presented on 75 cases of malaria, in 6% of which transient urticaria occurred. Blood smears showed 73 of these cases to be vivax, 1 falciparum, and 1 mixed vivax and falciparum. Transient urticaria occurred in 2 fresh and 3 recurrent infections in this group. The eruption varied from pin-head to half dollar in size and showed no special preference for location. Itching varied from severe to none. The eruption appeared and disappeared with the rise and fall of the fever. The 3 patients with recurrent malaria stated that they did not have urticaria during previous attacks. Only 1 patient had a history of previous urticaria and that was during an attack of scarlet fever 12 years before. Urticaria did not develop with every rise in temperature, perhaps being absent in the first or subsequent rigor, but it usually appeared regularly with each rise in temperature after its first appearance. The only drug used in these cases was codein sulfate by mouth, and this rarely causes urticaria.

A case is described of a 21 year old soldier admitted with headache, chills and fever which had continued for two days. He had not had either malaria or suppressive atabrine therapy. Physical examination showed no cause for the fever and 4 malaria smears were negative. A transient urticaria appeared the fourth day and lasted 12 hours. It developed with a sharp temperature rise and disappeared with return to normal. The patient was discharged because he had no fever or headache, although it was felt that he had malaria. Chills, fever and headache recurred the second, fourth and sixth days afterwards. There was no urticarial rash then but blood smear showed vivax malaria. 28 references.

Kala-Azar. 3 Cases Developing in Veterans. *J. P. Duffy and L. E. Davison, Crile Veterans Administration Hospital, Cleveland, O.* Am. J. M. Sc. 217: 21-27, Jan. 1949.

Three case reports of kala-azar occurring in veterans of World War II were presented. The clinical picture and response to specific therapy was typical in each case. All patients had been in endemic areas, two in India and one in the Mediterranean area. The minimum incubation periods varied from 14 to 21 months. Leishman-Donovan bodies were demonstrated in the splenic substance by direct smear in two of the cases; splenic puncture was not performed in the third case. Leishman-Donovan bodies were not found in bone marrow or peripheral blood in any of the cases, but laboratory findings were otherwise typical. All were treated with neostibosan with a total dosage up to 7 Gm., given in daily intravenous injections of .3 Gm., and all showed progressive improvement, becoming afebrile on the tenth or eleventh day. They have been followed for periods of 13 to 27 months and have shown no evidence of recurrence. Attention is called to the fact that isolated cases may be seen in the United States and may be overlooked, unless the long incubation period is kept in mind. 6 references. 6 figures.—*Author's abstract.*

The Diagnosis of Schistosomiasis by Rectal and Vesical Snips Based on 150 Autopsies. *M. Gelfand and W. F. Ross, Government Medical Service, South Rhodesia.* J. Trop. Med. 52: 12-15, Jan. 1949.

Results are presented of a comparative study of rectums, bladders and mucosal snips from both organs in 150 cases known to be infected with *Schistosoma hematobium*, *S. mansoni*, or both. The rectum and bladder were removed from each case at autopsy, cut into small pieces and separately digested with 10% potassium hydroxide at 37° C. for twenty-four hours. The undigested tissue was separated by passage through a tea-strainer, the filtrate centrifuged and examined for ova with a 2/3 in. lens. Mucosal snips about 3/8 in. long and 1/4 in. broad were taken from each organ before digestion, teased out with dissecting needles in a drop of water on a slide, a cover-slip applied when sufficiently thin, compressed, and examined with a 2/3 in. lens for ova.

The rectums of 93% and the bladders of 91% of these cases showed ova on digestion. Ova of *S. mansoni* were found in 52% of the rectal snips and those of *S. hematobium* in 80% of the bladder snips. *S. hematobium* ova were found in 60% of rectal snips. These results confirm the value of rectal and bladder snips in diagnosing schistosomiasis. This method does not reveal all cases however.

Rectal schistosomiasis shows few, if any, characteristic lesions as does the vesical variety. A snipping should be taken from suspected cases even if the mucous membrane looks normal, however, and examined, as ova have been recovered in 30% of cases by digestion from normal appearing organs. The procedure should be followed in suspected cases when careful examination of several specimens of stool and urine are negative for ova and sigmoidoscopy or cystoscopy are negative. 6 references. 2 tables.

Acquired Resistance to Proguanil (Paludrine) in *Plasmodium Vivax*. *D. R. Seaton and E. M. Lourie, Liverpool School of Tropical Medicine, Liverpool, England.* Lancet 1: 394-95, Mar. 5, 1949.

Repeated observations on a Hong-Kong strain of *Plasmodium vivax* maintained in neurosyphilitics by syringe-passage showed that the least amount of paludrine which would abolish fever and parasitemia within 48 hours of the third dose was 1.25 mg. daily for three days. Resistance to paludrine was produced in this strain by giving repeated small doses of the drug before subinoculation to consecutive patients in a series in which the strain was maintained by blood inoculation. The resistance increased slowly, and by the twenty-seventh passage (85 weeks from the start of the investigation) the strain was unaffected by three consecutive daily doses of 100 mg. The resistance survived mosquito-transmission. It was considered most unlikely that the use of paludrine in the field would give rise to a serious degree of resistance to this drug in strains of *Plasmodium vivax*. 3 references. 1 table.—*Author's abstract.*

4. Respiratory Disorders and Diseases

On the Roentgenologic Picture of Pulmonary Edema. *S. Rennoes, Roentgen Department of the Oslo Municipal Hospital, Ulleral, Norway.* Acta Radiol. 30: 169-176, Aug. 31, 1948.

The roentgenographic picture of pulmonary edema has become known only recently, especially in the last 15 years. The essential findings are the following:

The heart is commonly enlarged and symmetrical patches of increased density are found. These are more or less confluent, usually in the perihilar regions, leaving the apices, peripheral borders and bases relatively clear. These opacities are ill defined, the bronchi stand out clearly, but the vascular markings are not seen. All these changes may be quite transitory.

In the differential diagnosis of this roentgenologic picture one must consider any other widespread bilateral shadows in the lung fields, especially bronchopneumonia or hemorrhagic infiltration. The latter, however, commonly involves the periphery also. The greatest difficulty in differentiation arises between pulmonary edema and passive pulmonary congestion. Typically the latter is associated with vascular filling, back pressure, perivascular and interstitial reaction, often a mitral heart configuration, enlarged hilar shadows. The vessels in passive pulmonary congestion stand out clearly whereas the bronchi are very poorly made out. As pointed out this is the exact reverse of the observations made in pulmonary edema.

In addition to the hilar density there may also be fine miliary opacities causing a fluffy mottling of both lung fields. Occasionally associated with pleural exudate there may be larger irregular soft shadows at the bases.

Three cases are presented with typical roentgenograms confirmed by autopsy findings.

Treatment of Asthma with Roentgen Ray Therapy *(Traitement de l'asthme par la radiothérapie.) P. Vallery-Radot and P. Blamoutier, Paris France.* Presse méd. 56: 813-14, Nov. 20, 1948.

After studying radiotherapy of asthma for 23 years it has become apparent that this form of treatment is not the ultimate or sole form to be advised, but a very useful and often successful adjunct. Over this period of time 680 patients with asthma were so treated and followed. The treatment was administered about 10 times; each time the patient was given 150-200 r to the thorax with an x-ray tube carrying 180 to 200 kilovolts, and considerable filtration.

Irradiation of other organs than the lungs is not ordinarily recommended, except rarely of the spleen, thyroid or ovaries, if there is any suspicion that these organs contribute to the trigger mechanism responsible for the asthmatic paroxysms. Usually, definite improvement does not appear until the seventh or eighth session, and occasionally a second course of 2000 r (total) has to be resorted to after a rest period of about 8 weeks. In some cases as much as 18,000 r have been given over an average of 110 sessions within 3 to 7 years. The treatment is well tolerated, and radiodermatitis or other systemic manifestations of any severity are rare.

Pulmonary tuberculosis is a strict contraindication to this form of therapy. The best results are obtained in older people suffering from pulmonary emphysema, with frequently repeated bronchitis, or significantly enlarged tracheobronchial nodes. Little can be expected in truly allergic asthma, in cardiac difficulties, anemias and other primary difficulties which cannot be modified by x-ray irradiation.

Of the total of 680 cases of "pure" asthma, 23% were greatly improved by radiotherapy, and 18% more "significantly improved." Twenty-three per cent showed only transient amelioration and 36% failed altogether.

The Value of Roentgenology in the Prognosis of Minimal Tuberculosis. *Archibald L. Cochrane, Harold W. Campbell and Samuel C. Stine, Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pa.* Am. J. Roentgenol. 61: 153-65, Feb. 1949.

An analysis is presented of the results from the prognostic viewpoint of the roentgenologist's opinion of activity at the time of first roentgenogram in 1,100 cases of minimal tuberculosis over the twenty year period 1926 to 1945. During the last ten year period, all diagnoses were classified when made as active, of questionable significance, and as inactive. Roentgenograms were read in the course of normal work and the patient's chart was usually available. Tables are given showing the ratio of progression rates and death rates per 100 person-observation years. The number of progressions and deaths for a five year period were finally selected as best for statistical treatments. There were no rules for determining the roentgenologist's errors but they were arbitrarily considered to include "inactive" cases which progressed in five years, cases "of questionable clinical significance" which progressed though untreated, and "active" cases which had treatment and did not progress. The first three groups constitute the minimal error in diagnosis.

Tables are given showing the score made by the Phipp's roentgenologist in comparison with a so-called "blind" or perfect roentgenologist. The perfect score was 100 and a score comparable to chance was 0. The score of the Phipp's roentgenologist was 80 for all sex and race groups in diagnosing inactive cases, but only 40 in cases of questionable significance and 41 for active cases which did not progress. Results of these studies show that there is considerable error in the roentgenologist's estimate of prognosis, but that the results are much better than would be expected from chance. This was especially the case in the error of diagnosis of inactive minimal tuberculosis. These results indicate that the roentgenologist's opinion of activity at the time of first roentgenogram is of great value in determining the type of treatment. 3 references. 12 tables. 2 figures.

Pulmonary Complications in Hodgkin's Disease and the Treatment. *L. F. Shryock, Enid, Oklahoma.* J. Oklahoma, M. A. 42: 8-10, Jan. 1949.

Pulmonary involvement is not rare in Hodgkin's disease. The mediastinal nodes are more frequently involved than other pulmonary structures, but the pulmonary parenchyma may also be invaded as it contains many lymphatic vessels and lymphoid collection. These parenchymal lesions often resemble carcinoma in the roentgenogram. Pleural effusion occurs less frequently; it may be due to direct involvement of the lymphatics of the pleura or to interference with the circulation by a mediastinal mass. Diagnosis can be made definitely only by biopsy of an involved superficial lymph node.

Four illustrative cases are reported showing involvement of the mediastinal nodes or the pulmonary parenchyma. One of these patients had pleural

effusion; autopsy in this case showed a mediastinal mass constricting the trachea and great vessels. In all these cases diagnosis was made by biopsy of an enlarged axillary or cervical node.

As in all cases of Hodgkin's disease, treatment is largely palliative. Roentgen-ray therapy is at present the treatment of choice. In one of the author's cases, the mediastinal lymph nodes and the axillary glands were involved; x-ray therapy with a dosage of 800 r to each axilla and 800 r to two anterior chest fields, directed to the mediastinum, resulted in almost complete regression of the lesions and complete relief of symptoms for nine months, after which other lymph nodes became involved. 7 references. 4 figures.

Pulmonary Hazard of the Ingestion of Mineral Oil in the Apparently Healthy Adult. A Clinicoroentgenologic Study, with a Report of Five Cases. *Louis Schneider, Mt. Vernon, N. Y.* New England J. Med. 240: 284-91, Feb. 24, 1949.

It has been known for some time that the repeated use of mineral oil in nose and throat medicaments may produce a chronic pneumonitis, the so-called lipid pneumonia. Likewise, such condition may result from the repeated ingestion of liquid petrolatum for laxative purposes by debilitated persons with defects in the integrity of the nervous system controlling the mouth and throat. It is not appreciated, however, that the ingestion of mineral oil for years by the apparently healthy adult may also produce lipid pneumonia.

The author describes five such cases occurring in older individuals and has appended briefly the histories of two more. Briefly, they are characterized, especially in the early stages by such paucity of symptoms and physical signs, that they may go undetected until they are picked up by one of the numerous case-finding Tuberculosis Surveys now being conducted on an ever-increasing scale. The x-ray appearance of the lesion may vary from a small ill-defined ground-glass density to a circumscribed uniformly dense process that the pathologists have called paraffinoma. Following the laws of gravity, this man-made disease in the ambulatory patient is naturally situated in the lower lobes, first on one side (usually the right), finally becoming bilateral after years of repeated aspiration of the mineral oil. The chief error in diagnosis, particularly when the pulmonary involvement is one-sided, is to mistake this benign granulomatous condition for broncho-pulmonary cancer. In this era of pulmonary resection, many a lung has been removed for cancer only to find it the seat of lipid pneumonia which was not thought of preoperatively. More of these cases will be diagnosed and saved from unnecessary operation if the existence of this disease is borne in mind by those interested in the clinicoroentgen aspects of chronic pulmonary disease. Among simple tests used in the diagnosis of suspected oil-aspiration pneumonitis are the examination of sputum for mineral oil droplets and the careful performance of lung aspiration when this not-innocuous procedure must be done.

In order to ascertain the real pulmonary hazard to the apparently healthy older adult who has been taking mineral oil for the relief of constipation for many years, an x-ray survey of such individuals on a large scale is under way. 18 references. 8 figures.—*Author's abstract.*

Primary Tularemic Pneumonia Treated with Streptomycin: Report of a Case. *Stephen L. Johnson, Evansville.* J. Indiana M. A. 42: 125-27, Feb. 1949.

A white male, 37 years of age, developed high fever, flushed face, headache and generalized aching. Nausea developed within twenty-four hours. A cough was initially present and became productive of purulent sputum; coughing was often followed by vomiting. The patient had handled rabbits a few days preceding the onset of symptoms.

The temperature was 104.6 F., pulse 112, respiration 24, and blood pressure 140/80. There was moderate conjunctivitis, and congestion of the nose and throat. Deep reflexes were all sluggish. The white cell count was 11,900 with 87% neutrophiles (including 13 band forms), 11% lymphocytes, and 2% monocytes. Acetone, albumin and casts appeared in the urine. The sputum contained mixed organisms with staphylococcus and streptococcus predominating. Roentgenograms showed a pneumonitis of the left lung. A marked stridor developed over most of the left lung. The initial treatment was oxygen, intravenous amigen, and penicillin because of mixed organisms in the sputum. There were no peripheral sores or palpable lymph glands. The temperature reached 104 F. daily. A careful history revealed that he might have acquired a primary inhalation exposure to tularemia. Agglutination for tularemia on the ninth day of illness was complete in 1: 200 dilution. The patient was given streptomycin, 2 Gm. per day. Symptomatic improvement followed. The agglutination titer was positive at 1:400 on the thirteenth day and 1:800 on the seventeenth day. Chest roentgenograms showed decreased consolidation before discharge. He received 11 Gm. of streptomycin in six days, and was discharged on the twentieth day of illness with normal temperature. Eight months later his pneumonia was found cleared except for a fine band of fibrosis but the costophrenic sinus was obliterated, suggesting pleural involvement.

The effect of streptomycin is on the toxicity of these patients. Roentgen improvement does not follow the clinical one. Pleural effusion may first appear while the patient is apparently recovering and may be persistent. 10 references. 1 figure.

5. Cardiovascular Disorders and Diseases

Necrotizing Generalized Arteritis Due to the Use of Sulfonamide Drugs. *T. G. Rijssel and L. Meyler, University of Groningen, Holland.* Acta med. Scandinav. 132: fasc. III, 251-54, Dec. 31, 1948.

Of the 7 patients (various infections) treated with sulfonamide, 6 died. No sepsis was noted. Leucocyte count up to 25,000 was seen in 5 cases. Symptoms of kidney impairment (nephritis, anemia down to 54% HB,

eosinophilia up to 62%, skin allergy, asthma) were present. Other symptoms included: polyneuritis, pains simulating arthritic aches, and, in one case, mental disturbance. Autopsy showed necrosis of the lobar artery (walls); in the heart, lungs, liver, etc. Smaller arteries and capillaries were similarly affected. Case histories were negative for tropical fever and acquired syphilis, hence, drug poisoning was clearly indicated.

Sulfa drugs are known to combine with the blood proteins, forming an antigen. An allergy results, by way of anaphylactic shock. Death follows. The patient dies in a state of primary shock, as in cases of intolerance to serum therapy.

Penicillin is less harmful, hence preferable. Sulfonamides should be used only when absolutely necessary. If temperature is not reduced within 48 to 72 hours, the drug is ineffective. A rise following an initial temperature drop shows intolerance. Urine volume below 1500 cc. (checked daily) and other allergic symptoms, call for discontinuance of drug. 13 references. 3 tables.

Modern Treatment of Edema. With a Report of Relatively Low Toxicity and Effectiveness of Thiomerin, a New Mercurial Diuretic that is Well Tolerated Subcutaneously. *George R. Herrmann, John W. Chriss, Milton R. Hejtmancik and Paul M. Sims, Jr., University of Texas Medical Branch, Galveston, Tex.* Am. Pract. 3: 393-99, March 1949.

Edema is the increase of intercellular or interstitial subcutaneous fluid to the point that we recognize swelling and pitting on pressure of the skin. There are usually abnormal accumulations of free fluid in the pleural or peritoneal cavities and sometimes in the pericardial sac that produce physical signs; disturbed salt and water exchange, acute nephritis, hypoproteinemia of nephrosis, or cirrhosis of the liver, and edema resulting from myocardial insufficiency.

Edema fluid should be removed. Successful treatment depends upon recognition of all the contributing factors that have upset normal salt and water balance.

The usual minimum water needs of a patient are 1,500 cc. per day for vaporization and stools and 1,500 cc. per day for urine. About 1,000 cc. of this is supplied in ordinary foodstuffs and an additional 2,000-3,000 may be ingested as fluids. The habits of individuals differ, but the average man has an intake of 5 to 10 Gm. sodium each day with food.

In edematous states the tissues seem to cling tenaciously to sodium salt. A tendency to acidosis from acid-yielding foods or ingested acid salts withdraw Na to form a neutral base.

The dietetic management of edema is of importance mainly in restricting the Na intake in both food and fluids.

In recent years some serious and a few fatal reactions have been reported with increased myocardial irritability and acute cardiac depression following intravenous mercurial injection. A less irritating and less toxic mercurial succinyl urea compound with theophyllin was developed as mercuhydrin. Mercuhydrin caused no pain when given intramuscularly and was found to be potent and well tolerated. In toxic doses in dogs, mercuhydrin was found by Chapman and Shaffer to produce cardiac standstill. Clinically, the usefulness of mercurial diuretics in the treatment of edema due to myocardial insufficiency and to the hypoalbuminemia of nephrosis and cirrhosis of the liver has been recognized. Since mercury was demonstrated to cause myocardial poisoning, the war-born BAL (dimercaptopropylpropanol) with two sulfhydril radicles was logically introduced with mercurial diuretics to prevent the cardiac toxic mercurial action, but this also stopped the diuretic action. Chemists then combined a single sulfhydril radicle with an organic mercury compound and succeeded in developing a less irritating and consequently less toxic diuretic. This compound has been given the name of Thiomerin.

Thiomerin has been found to be 160 times less toxic than mercuhydrin and just as effective. In addition, it was found to be less irritating and could be injected subcutaneously without causing significant pain. Thiomerin has produced no cardiac toxic action or renal irritation, no acidosis, no significant salt depletion, and no side effects in our extensive experimental and clinical investigation. The results of our preliminary studies are most encouraging.

We have used Thiomerin since March 1948. It has been injected subcutaneously in 200 patients and intravenously in 50 patients with congestive heart failure and edema or paroxysmal nocturnal dyspnea resulting from hypertension, arteriosclerotic, syphilitic or rheumatic heart disease. The drug was given in 0.5 to 2 cc. doses 1 to 15 times in various patients at intervals of 5 to 7 days for as long as nine months or daily up to 5 days in succession without producing any renal or cardiac irritation or complication.

In 20 patients ammonium chloride was given, and it was found to be effective after very small doses subcutaneously. We have made electrocardiographic studies just before, during 1, 2, 3, 4, and 5 minutes after intravenous Thiomerin injections in 100 cases and have found considerably fewer myocardial reactions (2-5% at the most). 22 references. 1 table.—*George R. Herrmann.*

Cardiac Asthma. Acute Cardiac Dyspnea. *Leon Unger, Northwestern University Medical School, Chicago, Ill.* Quart Bull. Northwestern Univ. M. School. 23: 130-35, Spring 1949.

The case is reported of a man about 55, with a blood pressure of over 200 and with albumin and casts in the urine, and mild anemia. A series of attacks occurred usually 2 to 4 a.m., with gasping for breath, orthopnea, pallor and rapid pulse. Examination revealed groaning sounds or "wheezes." Fear was marked. A little cough and frothy and, at times, bloody sputum

occurred. Numerous moist rales were heard at the bases of both lobes posteriorly. During these attacks, the heart was markedly dilated. Between attacks, the diameter of the heart returned to its original rather large size. Relief was obtained by the use of ¼ grain of morphine hypodermically, sometimes repeated. The final attack occurred suddenly and without medical attendance. Autopsy was not obtained. This case is typical of "cardiac asthma," and many similar ones with a high mortality rate have been observed.

"Cardiac asthma" is a term widely used to describe an acute attack, characterized by dyspnea, coughing and slight wheezing. It is probably due to sudden failure of the left ventricle. It is due directly or indirectly to heart disease. In my opinion, it is not an allergic condition. It is very rare in rheumatic heart disease. Attacks of cardiac asthma always occur because the left ventricle suddenly fails; this causes sudden engorgement of the lungs. Sleep and lying down are important factors but we do not know exactly why. Fishberg believes that "with a weakened left ventricle, the recumbent position predisposes to pulmonary engorgement because it entails a shift of blood from the abdomen and lower extremities to the lungs. And the diminished sensitivity of the nervous system during sleep perhaps allows this engorgement to attain a higher degree than would otherwise occur."

While some believe that cardiac asthma is allergic or associated with allergy, I have found no evidence of allergy in my cases of cardiac asthma. All of these patients had cardiac or cardiorenal diseases prior to and associated with the paroxysmal attacks. I have never seen a patient with bronchial asthma develop cardiac asthma. Heart disease and bronchial asthma can and do coexist, and one may aggravate the other.

The differential diagnosis between bronchial asthma and cardiac asthma is pointed out in the following table:

	Bronchial Asthma	Cardiac Asthma
1.	Paroxysmal dyspnea (allergic)	Paroxysmal dyspnea (cardio-renal)
2.	History of previous attacks	Attacks very few
3.	Obstruction lower air passages	Pulmonary edema (failure left ventricle)
4.	Onset in early life, usually	Onset after 40, usually
5.	Allergy in patient and family, usually	Hypertension, coronary disease, aortic regurgitation, chronic nephritis
6	Eosinophilia in blood and sputum, usually	Absent
7.	Wheezing, prolonged expiration all over lungs	Moist rales, especially at bases, some coarse wheezing
8.	Warm perspiration	Cold clammy skin
9.	Condition usually good	Often in shock
10.	Heart usually small	Heart dilated
11.	Pulse good	Pulse often thready, irregular
12.	No fear of death, usually	Fear of death
13.	Epinephrin and/or aminophyllin usually gives relief; morphine dangerous	Morphine best, also venesection, epinephrine bad.
14.	Positive skin test, usually	Negative
15.	Elimination of cause gives relief, often complete	Rest in bed, etc., prolongs life
16.	Circulation time normal	Circulation time usually prolonged

The prognosis is poor, as death usually occurs after relatively few attacks.

Treatment must be prompt and efficient. Morphine is the best drug. It should be given hypodermically and repeated if necessary. Venesection, inhalation of oxygen and the use of digitalis are also valuable. In between attacks, the usual cardiac measures may be necessary, e.g., restriction of salt and fluids, and the use of ammonium chloride and mercurial diuretics.

The place of aminophyllin is disputed. This drug gives marvelous results in most attacks of bronchial asthma, but its value in cardiac asthma has by no means been established. Some inject it intravenously, but many of us believe that the intravenous use of aminophyllin should be restricted to patients with bronchial asthma; here we have a clear cut indication with practically no danger. I believe that in cardiac asthma, if used at all, it should be given orally, per rectum, or intramuscularly; the intravenous route is decidedly dangerous.

Epinephrin should not be given to these cardiac patients, though it seems to help in a few cases. The prompt injection of morphine remains the best treatment for cardiac asthma. 22 references. 1 table.—*Author's abstract.*

Psychological Phenomena in Cardiac Patients. *Carl Binger, Cornell University Medical College.* Bull. N. Y. Acad. Med. 24: 687-701, Nov. 1948.

Some of the psychological phenomena seen in cardiac patients are discussed, especially with reference to three ages groups: (1) children and young people who suffer from various forms of rheumatic heart disease; (2) people of early and middle age who suffer from so-called "cardiac neuroses"; (3) people of middle and late middle life who suffer from coronary insufficiency and coronary occlusion. Anxiety is the most important psychological manifestation in cardiac patients. In the first group it is more to be reckoned with in the parent than in the sick person. In the next group anxiety is of cardinal importance in the patient himself and in the formation of his symptoms. Usually in the "cardiac neuroses" it is necessary to differentiate between hypochondriasis, anxiety neuroses, and organ neuroses, and sometimes hysteria, in its technical, not its popular sense. None is necessarily exclusive of the other but the indications for treatment depend upon the weighing of these various components. In all of them anxiety plays the predominant dynamic role. The anxiety is not entirely equivalent to fear and legitimate worry, but it is a complicated emotional state in which hostility or rage as a defense against fear is also mobilized. The psychiatrist must make up his mind whether to explore and uncover the deeper sources of anxiety or whether to help his patient cover them up and let healing occur by repression. The choice will depend upon the age, adaptability, intelligence and strength of character of the patient and on his capacity and willingness to relinquish symptoms. In the older age groups effective psychotherapy is by no means ruled out, but it is often difficult, especially in the presence of extensive cerebral arteriosclerosis. Although these patients have outspoken structural damage to their hearts, it would be a mistake to conclude that

emotional influences play no role in their illness or in their recovery. There is no better psychotherapy for the cardiac invalid than to be permitted and encouraged to exercise when such advice is compatible with his cardiac reserve. 11 references.

Clinical Observations with Fagarine. *D. Scherf, A. M. Silver and L. D. Weinberg, New York Medical College, New York, N. Y.* Ann. Int. Med. 30: 100-20, Jan. 1949.

Fagarine (alpha-fagarine hydrochloride), an alkaloid extracted from the plant, *Fagara coco* (Apotarg Laboratory, Cordoba, Argentina) has been recommended for use in some cardiac irregularities. It was initially used in man by A. C. Tacquini, and the appearance of multifocal ventricular extrasystoles in 1 of 7 cases prompted our restriction of the drug to hopelessly ill patients and limited dosage to less than 2 mg. per kilogram.

Fagarine was used fourteen times in 13 patients between 45 and 94 years of age, of whom 8 were over 70. All had some disturbance of cardiac rhythm; 7 had auricular fibrillation and 3 auricular flutter. In 1 case flutter disappeared immediately before the injection and in another, only sinus tachycardia was present. In 6 of the remaining 11 cases sinus rhythm was reestablished. In 1 case of long standing fibrillation, this disappeared at some time within ten hours, although not within the two hour observation period.

One case of heterotopic tachycardia originating above the bifurcation of the conduction system showed slowing of the ventricular rate first and later bradycardia with idioventricular rhythm. The next morning, however, the original arrhythmia had reappeared as might be expected in certain tachycardias *(extrasystolies à paroxysms Tachycardiques)*.

In a case with auricular fibrillation in thyrotoxicosis, though sinus rhythm was rapidly established, auricular fibrillation recurred within the succeeding two days.

In the last 2 cases the use of the drug resulted in fatalities. In the first, an attack of Stokes-Adams syndrome was caused by ventricular flutter within five minutes after the intramuscular injection, and ventricular fibrillation followed temporary restoration of sinus rhythm. The rapidity of onset made it seem that the poor condition of the patient was responsible for this reaction. A thyrotoxic patient in somewhat better condition was given a much reduced dose, but lethal ventricular fibrillation developed before auricular response was seen. The investigation was stopped at once.

Multifocal extrasystoles are always an ominous sign. They occurred in 5 patients besides the one in whom ventricular fibrillation developed. In the case receiving the medication twice, 0.06 Gm. caused no response, while 0.08 Gm. was followed by ventricular extrasystoles. QT prolongation, ST segment depression and lowered T waves were seen.

In 1932 fagarine was observed to raise the threshold of the heart to fibrillation after faradization and to diminish the risk of ventricular fibrillation after coronary vessel ligation. Previous digitalization is a contraindication to fagarine, but where quinidine and digitalis fail, a drug to arrest a heterotopic tachycardia may be necessary.

As fagarine has not proved to be adequately safe or efficient, related drugs should be further investigated. Fagarine has proved to be of outstanding value in dogs where high doses intravenously abolish auricular fibrillation safely without rhythmic changes or extrasystoles, and some variants may be equally useful in man. 12 references. 1 table. 11 figures.—*Author's abstract.*

The Bioassay of Adrenal Corticoids in the Urine of Patients with Congestive Heart Failure. *Alvin E. Parrish, George Washington University School of Medicine, Washington, D. C.* J. Clin. Investigation 28: 45-49, Jan. 1949.

The urines of 10 patients with congestive heart failure were studied for the presence of adrenal corticoid substances and compared with the urine of 6 normal individuals. Extracts were made by the method of Venning, Kazmin, and Bell. These extracts were assayed by using the survival time of adrenalectomized rats as one method of assay and the ability of the extracts to produce glycogen-storage in the livers of adrenalectomized rats as another. Of the 10 patients, 4 showed an increase of corticoids over that found in normal urines which prolonged the life of adrenalectomized rats. These four were the most seriously ill. An increase in corticoids with glycogenic activity was also observed in the urine obtained from patients with heart failure. Based on what is already known about congestive heart failure, it was felt that this increase in corticoids represented a result rather than a cause of the symptoms of heart failure, unless it is postulated that the adrenal corticoids act on the renal vascular system. 30 references. 3 tables. —*Author's abstract.*

Conditions Which Result in Increased Pressure Within the Lesser Circulation. *C. Allen Good and Thomas J. Dry, Mayo Clinic, Rochester, Minn.* Am. J. Roentgenol. 61:26-29, Jan. 1949.

Hypertension within the lesser circulation has many causes. The signs of pulmonary hypertension seen by the roentgenologist are enlargement of the pulmonary arteries and of the outflow tract of the right ventricle, and enlargement of the right side of the heart. If pulmonary valvular incompetence results, exaggerated pulsation of the pulmonary arteries in the hilus of the lung may also occur. The earliest sign is enlargement of the pulmonary artery and pulmonary conus. The arterial branches in the hilus may appear dilated.

Right ventricular enlargement appears on posteroanterior films as enlargement of the cardiac shadow on the left. The diaphragmatic cardiac segment, in the left anterior oblique position, is enlarged and its ventral

border is rounded. Left ventriclar enlargement, in this position, produces rounding of the dorsal border of the cardiac shadow. If the tricuspid valve becomes incompetent and the right auricle dilated, the heart shadow enlarges to the right.

The most common causes of pulmonary hypertension from obstruction beyond the pulmonary system are mitral stenosis and a failing left ventricle; the vessels are overloaded and the efferent lung flow is impeded. In addition to enlargement of the conus, mitral stenosis produces left auricular enlargement, best seen by posterior displacement of the barium-filled esophagus in the right anterior oblique position.

Within the pulmonary circuit there may be obstruction at different levels. The main vessels may be occluded by an embolus or thrombus; the medium-sized branches may be occluded during sickle cell anemia, schistosomiasis, or metastatic carcinomatosis; the arterioles may become sclerotic or close with many pulmonary diseases; the capillaries may be obstructed in emphysema or in pulmonary fibrosis.

Abnormal blood shunts from the arteries are usually congenital, such as patent ductus arteriosus, interatrial septal defect, and Lutembacher's syndrome. Rarely, an aortic aneurysm ruptures into the pulmonary artery.

Kyphoscoliosis probably causes pulmonary hypertension because the deformity produces atelectasis and emphysema.. Pulmonary embolism is an important cause, but it may produce misleading clinical symptoms. In many instances there are signs of acute cor pulmonale, including dilated pulmonary vessels in the hilus, enlarged conus shadow, and enlarged heart. A roentgenological diagnosis of pulmonary embolism based on signs of hypertension is often possible before there are roentgenological signs of pulmonary infarction and pleural reaction. 13 references. 1 figure.

The Application of an Oximeter for Whole Blood to Diagnostic Cardiac Catheterization. *Dale Groom, Earl H. Wood, Howard B. Burchell and Robert L. Parker, Mayo Foundation, Rochester, Minn.* Proc. Staff Meet., Mayo Clin. 23: 601-609, Dec. 22, 1948.

Measurements of the oxygen saturation of blood, which heretofore have been made almost exclusively by the Van Slyke method of gasometric analysis, can now be accomplished quickly and economically on whole blood with a clinically useful degree of accuracy by means of a photoelectric oximeter. The physical basis of this new method is the differential light absorption characteristics of oxyhemoglobin and reduced hemoglobin in the red and near infra-red regions of the spectrum, and photoelectric measurement of concentration of these blood pigments in terms of their transmission of light according to Beer's law.

The oximeter is capable of instantaneous and continuous determination of oxygen saturation of whole blood independent of its hemoglobin content. Saturation can be recorded photographically, synchronously with recordings

of other physiologic variables. The whole blood oximeter has been used in more than 60 diagnostic cardiac catheterizations at the Mayo Clinic and in studies of the oxygen saturation of arterial blood in man. It is concluded that this instrument is a useful and valuable adjunct to the catheterization technique, and that it may find widespread application in other clinical and research studies. 25 references. 2 tables. 3 figures.—*Dale Groom.*

Left Atrial Calcification in Rheumatic Heart Disease. *Bernard S. Epstein, The Jewish Hospital of Brooklyn, Brooklyn, N. Y.* Am. J. Roentgenol. 61: 202-8, Feb. 1949.

Report is presented of 3 patients having rheumatic heart disease, with mitral stenosis and insufficiency, in whom calcification of the left atrial endocardium outlining the chamber to a greater or less degree was identified and studied during life. Thickness of the calcification measured up to 2 mm. in these cases, heaviest deposits being on the posterior and left lateral walls of the left atrium. Associated mitral valve calcifications were seen in 2 of these cases. The relative positions of the left border of the heart and the left side of the left atrium were well seen, confirming the fact that the latter does not usually form the left border of the heart with dilatation of the chamber. Study in the right anterior oblique position confirmed the close approximation of the barium-filled esophagus and posterior aspect of the left atrium, but this only occurs at the point of greatest convexity of the dilated atrium, indicating that the esophageal indentation does not necessarily show the exact contour of the dilated atrium. The atrium is appreciably separated from the esophagus above and below. The left main bronchus was not elevated in these 3 cases, showing that this sign may be absent with left atrial dilatation.

Left atrial calcification should be easily differentiated from other cardiac calcification. Valvular deposits are identified by their position and characteristic movements. Myocardial calcifications usually have an amorphous appearance which may vary considerably in size and appearance. Coronary calcifications are usually linear, sometimes hard to identify, and may be seen at the left atrioventricular junction in both frontal and right anterior positions. Pericardial calcifications are usually seen over the apex, middle and lower segments of the left cardiac border or the diaphragmatic surface. The calcifications are best seen roentgenographically on overexposed films or very short exposures made with a Potter-Bucky diaphragm. 16 references. 3 figures.

Menstrual Syndrome in Mitral Stenosis (*Syndrome menstruel de la sténose mitrale*). *R. Lutembacher and J. E. Galimard, Paris, France.* Presse méd. 56: 885-86, Dec. 18, 1948.

For some time the authors have carried out studies of the relation of the functional difficulties observed in women with mitral lesions to the menstrual cycles. The syndrome commonly observed is characterized by the appearance

of exertional dyspnea, orthopnea and paroxysmal nocturnal dyspnea with pulmonary edema all appearing on a certain day in the menstrual cycle, though the day varies from patient to patient.

Other signs observed have been painful engorgement of the breasts and occasional visible dependent edema of the extremities. Rarely there was blood-tinged frothy sputum, and paroxysmal tachycardia. The general retention of water was evidenced by a significant gain in weight at the time of the reaction. This commonly increased during the premenstrual phase of the cycle, reaching its maximum 1 to 2 days prior to the onset of menstrual bleeding and ceasing with it. On other occasions, another bout of symptoms might start with the end of menstruation.

Experimentally, it has been possible on a number of occasions to reproduce the symptom complex in women with mitral stenosis by the administration of estrogens. A method is described which permits a direct estimation of estrogen content of the serum by comparing the refractory indexes of the test serum with a standard. In the cases showing excess of estrogen at the time of their attack administration of postpituitary hormone successfully controlled them. In other instances it has been necessary regularly to limit the intake of water and salt during every period preceding the expected time of the attack. Occasionally antihistaminic agents have been useful. 0 references.

Acute Bacterial Endocarditis Involving Both Mitral and Aortic Valves, Propagated across the Interventricular Septum. *(Endocardite ulcerovégétante mitroaortique — propagation interventriculaire). R. Lutembacher*, Paris, France. Presse méd. 57: 37-38, Jan. 5, 1949.

Ulceration and destruction of valves predominate in acute bacterial endocarditis. Occasionally the inflammatory processes pass through the interventricular septum, either by interstitial inflammation or by frank perforation. Perforation of the septum is rare, but a number of instances have been reported in the course of ulcerative endocarditis. Perforation takes place usually in the membranous septum.

The formation of aneurysms of the mitral valve is observed not uncommonly. At the point of insertion of the valve, leaflets vegetations appear on the septum. Simultaneously they have also been observed at the line of insertion of the tricuspid leaflets, and in the right auricular appendage. The involvement of the membranous portion of the interventricular septum by the inflammation commonly forms the basis of the sudden death of these patients from asystole, perhaps due to involvement of the neighboring bundle of His.

These ulcerovegetative forms of endocarditis are likewise characterized by the very great frequency of embolic phenomena. The vegetations are exceedingly fragile and break off readily. This is in contrast to the vegetations in most cases of subacute bacterial endocarditis where organization of vegetations is usually firm.

Two cases are described in detail in which pneumococcal acute endocarditis rapidly resulted in perforation of the septum, with very sudden death, attributable to sudden block of the bundle of His, without any preceding electrocardiographic abnormalities.

Observations on the Frequency of Paroxysmal Auricular Tachycardia *(Remarques sur l'étiologie de la tachycardie paroxystique). C. Lian and A. Cioni, l'Hôpital de la Pitie, Paris, France.* Presse méd. 57: 73, Jan. 15, 1949.

Paroxysmal auricular tachycardia is commonly believed to be found most frequently in young adults. A series of 29 cases compiled by Sir Thomas Lewis indicates, however, that only 10 of the 29 cases had their first attack under the age of 30.

A statistical study of the records of 342 cases of paroxysmal tachycardia indicated the following. Less than one third of all cases had their first attack under the age of 30. The greatest number experienced it between 30 and 50 years of age. The frequency was equal between the ages of 11 and 20 and the ages of 51 and 60. This emphasizes again that the first attack of paroxysmal tachycardia occurs much more frequently in advanced age than is commonly believed. The frequency was slightly greater in women, under the age of 40, and in men over that age. The total numbers were equal in the two sexes.

The incidence of cardiac disease coexisting with paroxysmal tachycardia was investigated in a smaller group. In 13% of 84 cases there was clinical evidence of valvular disease, and in an additional 12%, hypertension might have been present, judged by the presence of persistently elevated systolic pressure.

Streptococcal Subacute Bacterial Endocarditis: Cure of the Infection by Penicillin. Death from Continuing Inflammation with Cardiac Arrest. *(Endocardite à streptocoque. Guérson de l'infection par la pénicilline. Mort par a systolie inflammatoire). M. Roch, Medical Clinic, Geneva, Switzerland.* Progrès méd. 76: 243-244, May 24, 1948.

The advent of penicillin has revolutionized the therapy and prognosis of subacute bacterial endocarditis. In spite of its miraculous successes, however, this drug does not cure everything. A case in point is reported.

A 49 year old accountant with many hypochondrical complaints over many years but without any serious organic disease, developed fever, cough, weakness and nightsweats. He attributed these complaints to his neurasthenia and continued his work for several days, but finally reported to the hospital. There the main findings were an enlarged spleen, slightly enlarged heart with both systolic and aortic diastolic murmurs, and a marked anemia, without leukocytosis. Repeated blood cultures yielded a non-hemolytic streptococcus.

Treatment was started with 500,000 units of penicillin per day which lowered the fever to 38° C. for 2 weeks. Subsequently, 1 million units daily

for three weeks suppressed the fever completely, blood cultures were sterile, the patient felt well, and gained weight. He left the hospital and returned to work.

Follow-up examination during the subsequent months indicated persistently negative blood cultures and a satisfactory physical status except for the increase in loudness of the aortic diastolic murmur and a fall in diastolic blood pressure from 145/75 to 170/45. The sedimentation rate was slow, there was no evidence of continuing infection on the heart valves and the progressive changes were attributed to scarring of the valves in the healing process.

Gradually, the patient began to develop anginal pains and increasing evidence of cardiac failure, with paroxysmal nocturnal dyspnea, orthopnea, cough, and slight dependent edema. He had to abandon physical activity more and more, but continued with his work as an accountant. Finally, he re-entered the hospital 11 months after cure of his endocarditis, in rather marked left cardiac failure. He responded to cardiac therapy moderately well, but suddenly died without obvious cause.

Post mortem examination revealed an enlarged heart, with greatly hypertrophied left vertricle, and some pulmonary edema. The aortic valves were found thickened and deformed, with multiple perforations. At their border there were irregular endocardial nodules, of reddish color, but no vegetations suggestive of bacterial infection.

These nodules were evidently of inflammatory nature. In the absence of any bacterial infection at the time of death, the inflammatory activity was attributed to an allergic phenomenon. Other instances are recalled where aseptic endocarditis of the hypersensitivity type (? Limban-Sacks) followed the healing of subacute bacterial endocarditis. Up to 30% of patients cured of this infection by antimiotic therapy subsequently succumb to cardiac failure due to the mechanical difficulties produced by the scarred valves. It is not certain in how many such casualties the inflammation of hypersensitivity may contribute to perpetuating the inflammatory process and to aggravating the valvular deformity, not to speak of the possible myocardial involvement.

(A substantial number of cases similar to the one reported here have been observed in this country. In spite of the elimination of the active infection by means of antibiotics, death may occur within a few weeks or months from myocardial insufficiency associated with increasing deformity and mechanical insufficiency of the valves involved.—ED.)

Development of Cardiac Murmurs in Successfully Treated Cases of Bacterial Endocarditis. *Richard T. Beebe and John K. Meneely, Jr., Albany Medical College, Albany, N. Y.* New England J. Med. 240: 372-73, Mar. 10, 1949.

The presence of cardiac murmurs as an aid in the diagnosis of subacute bacterial endocarditis has been stressed in the past. A number of authors have emphasized that the absence of a murmur may be just cause for eliminat-

ing the diagnosis of subacute bacterial endocarditis. In the two cases that were reported, the diagnosis was essentially fever of undetermined origin for a period of days to weeks, at the end of which time there developed the typical murmurs heard in subacute bacterial endocarditis in association with positive blood cultures and petechiae. One case of acute bacterial endocarditis also behaved in a similar fashion. All three cases were cured by penicillin and have permanent murmurs. It is suggested that the absence of cardiac murmurs need not militate against the initial diagnosis of subacute bacterial endocarditis, and this diagnosis should be considered in all cases of fevers of undetermined origin. 3 references.—*Author's abstract.*

Splenectomy for Infarction of the Spleen Occurring in the Course of Subacute Bacterial Endocarditis. *(Splénectomie pour infarctus de la rate au cours d'une maladie d'Osler.) D. Giraud, A. Camelin, H. Farnung and A. Tarel, Lyon, France.* Presse méd. 56: 866-867, Dec. 11, 1948.

The prognosis of subacute bacterial endocarditis has been modified greatly by the advent of antibiotic therapy, particularly penicillin. Nevertheless there is one group of cases of this illness in which the chance of cure is not great. These are the cases of primary involvement of the aortic valve, frequently with negative blood cultures. Furthermore, penicillin does not protect any patient with subacute bacterial endocarditis from embolic phenomena while under treatment. The majority of such embolic disorders are inconsequential, but an occasional arterial embolism may be serious and lead to the necessity of amputating a limb. Small splenic infarcts are commonplace in the course of subacute bacterial endocarditis and of little consequence. Occasionally large splenic infarcts result in gangrene and serve as an accumulation of pus which interferes with cure by penicillin. Two illustrative cases are reported.

A 27 year old man had attacks of acute rheumatic fever in 1946 and 1947. Soon, thereafter, high fever with chills, signs of aortic incompetence, proteinuria and nitrogen retention developed. There was no response to salicylates and the blood culture was negative. Penicillin therapy was started (1 million units per day), without significant alteration of the fever curve. Six days later the patient experienced a severe left subcostal pain with a fever of 41° C. The intense pain with spasm of abdominal muscles made examination of the region impossible. The patient continued to get worse in spite of all therapeutic attempts and died one month later. At autopsy the spleen was not found, but in its place a large mass of gangrenous, putrid material, with multiple adhesions of abdominal organs. Vegetations were present on the leaflets of the aortic valve but nowhere else. It was concluded that the patient succumbed to the effects of a splenic infarct.

The second patient was a 21 year old man with a congenital heart lesion in whom fever, dyspnea and sudden severe left subcostal pain developed. The diagnosis of subacute bacterial endocarditis (on the basis of a congenital lesion) and of splenic infarct was made. In view of the experience with the first patient, this patient was placed on 2 million units of penicillin daily, and splenectomy was performed. All blood cultures remained negative. The operative specimen revealed a spleen somewhat enlarged with 3 large zones of infarction. The postoperative course was uneventful up to the date of the report. There was no recurrence of fever of embolic phenomena.

These cases illustrate that a patient under treatment for subacute bacterial endocarditis can support a splenectomy without difficulty and that such an operation may be life saving in the presence of a large septic splenic infarct. This gives rise to an abscess that penicillin cannot control or cure. Splenectomy should therefore be seriously considered in the face of evidence suggesting a large splenic infarct in subacute bacterial endocarditis. 7 references.

Visualization of Patent Ductus Arteriosus Botalli by Means of Thoracic Aortography. *G. Jonsson, B. Broden, H. E. Hanson, and J. Karnell, Soderjukhuset Stockholm, Sweden.* Acta Radiol. 30: 81-90, Aug. 31, 1948.

Since the introduction of angiocardiography by Steinberg and his group ten years ago, many cases of suspected patent ductus arteriosus have been examined by that method. It has been the common experience that the ductus is visualized poorly or not at all and that the deformity of the aorta that is commonly encountered may represent the effect of non-specific traction and not necessarily the infundibulum.

In view of this unsatisfactory situation the use of retrograde arteriography by various technics has been suggested. The method found most suitable is that previously successful in the demonstration of coarctation of the aorta. It consists essentially in catheterization of the radial artery so that the tip of the catheter comes to lie in a suitable position in the ascending aorta, often the sinus of Valsalva. The injection of contrast material which is performed rapidly is easy, because of the lack of organic obstruction or limitation.

Two cases are presented in which this examination was performed. The physical findings and radiographic appearance were suggestive but not altogether conclusive. The injection of radioopaque material into the ascending aorta outlined the patent ductus clearly in both cases and paved the way for surgical exploration. During operation, the findings were fully confirmed.

A third case with a continuous thrill and murmur in the second left interspace and a blood pressure of 140/55 presented the problem of an interarterial communication without good localization. Contrast substance passed from the aorta to pulmonary artery near the base of the heart, and the findings were confirmed at operation.

Pitressin Test. Usefulness in the Differential Diagnosis of Chest Pains. *Michael Bernreiter, St. Mary's Hospital, Kansas City, Mo.* J. Missouri, M.A. 46: 102-107, Feb. 1949.

A study was undertaken to evaluate the efficacy and safety of the "Pitressin Test" in the differential diagnosis of chest pains. 2 cc. (40 Pressor units) of Pitressin were given intramuscularly in the forearm. An electrocardiogram was taken before the injection and 4, 8, 12 and 15 minutes after it. The test was considered positive (presumptive evidence of insufficient coronary circulation) if one of the following criteria was met:

1. The arithmetic sum of the RS-T deviations in all four leads is 3 mm. or more.
2. A positive T-1, T-2 or T-4 changes to a flat diphasic or negative wave.

The Pitressin Test was performed on twenty cases in which the existence of coronary insufficiency could not definitely be established or excluded. The test was positive in five cases (25%). A positive test affords conclusive evidence of coronary insufficiency, a negative test does not exclude it.

Two patients developed chest pain before the test was completed and nitroglycerin sublingually gave prompt relief. Other side reactions (intestinal cramping, urgency to void and defecate) were easily controlled with seconal 0.1 Gm. and a tourniquet applied above injection to slow the absorption of Pitressin.

The test is safe, simple and of definite help in the differential diagnosis of conditions producing chest pain. 6 references. 6 figures.—*Author's abstract.*

The Management of Acute Coronary Occlusion with Myocardial Infarction. *George Burch, Tulane University School of Medicine, New Orleans, La.* South. M. J. 42: 186-93, March 1949.

There has been no truly significant advancement in recent years in the understanding of the problem of acute coronary occlusion. Probably the most important developments have been concerned with unipolar precordial exploratory electrocardiography and educational training in diagnosis and treatment of the condition. It is important to refrain from overtreating a patient with acute coronary occlusion — a common clinical error. Most patients will survive the episode, especially their first one, if they are treated conservatively.

A method of management of acute coronary occlusion is outlined. There is need for considerably more investigation of the pathogenesis and management of coronary occlusion. 26 references.—*Author's abstract.*

Dicoumarol Therapy of Acute Coronary Thrombosis. *David B. Carmichael (Lt. j.g., M.C., U. S. N.) and Henry K. Getting.* U. S. Nav. M. Bull. 49: 12-28, Jan.-Feb. 1949.

The treatment of 30 cases of acute coronary thrombosis with dicoumarol and of 43 control cases given the accepted routine treatment for coronary

disease are discussed. Previous hyperpiesis existed in about 45% of the patients. About 1 of every 5 patients in the control and 1 of every 3 in the treated group had had at least one previous attack of coronary thrombosis. The patients taking digitalis before their attack or needing it during their hospitalization or within three months afterwards are analyzed because of the part digitalis might take in immediate convalescence and because the amount of digitalis required for congestive heart failure would indicate whether dicoumarol caused more functional cardiac impairment than routine treatment. It was found that 43.9% of the control patients and 43% of the dicoumarolized patients required digitalis. Thrombo-embolic complications developed in 27.9% of the control patients but in only 6.7% of the dicoumarolized patients, indicating that it was safer to give digitalis to the latter group.

Dicoumarolized patients were given strict bed rest for only 30 days and hospitalized for only just over 5 weeks as compared with 34.8 days and 6 weeks for control patients. All patients making an uncomplicated recovery were given absolute bed rest for a minimum of 25 days. This is less than generally considered necessary and is in accordance with experiments showing that animals kept at prolonged rest after experimental myocardial infarction did not do as well as those allowed activity twice daily. The difference between the period of restricted activity and the average durations of bed rest and hospitalization is because of complications delaying recovery. The apparently decreased time required by dicoumarolized patients is because of the lower incidence of thrombo-embolic complications. Serious hemorrhage rarely occurred with dicoumarol therapy. The prothrombin concentration was 30% of normal or less in 53.6% of patients within 36 hours after commencing dicoumarol treatment, indicating that larger doses would perhaps be better during the first 48 hours in order to try to obtain a higher percentage of satisfactory levels during the initial stage of treatment.

The mortality rate of the dicoumarolized patients was 13.3% and of the control group 16.3%. The apparently good results obtained by dicoumarol therapy in myocardial infarction indicates that all such patients who are otherwise suitable should be given anticoagulant therapy as part of their treatment. 42 references. 4 tables.

Vitamin E in the Treatment of Angina Pectoris. *Iver S. Ravin and Kermit H. Katz. Boston University School of Medicine, Boston, Mass.* New *England J. Med.* 240: 331-33, Mar. 3, 1949.

There has been considerable interest among both physicians and patients since the announcement that Vitamin E might be therapeutically effective in heart disease was released in *Time* magazine in June, 1946.

Although Vitamin E has been investigated for many years and considerable knowledge has been accumulated regarding its chemical and physical properties, little is known about its function. All green plants have demonstrable amounts of the vitamin, and it is practically impossible to produce experimental deficiency in animals if any natural foods are present in the diet. Many different types of changes occur on deficiency diets, depending on which animals are used. No studies have been made on human beings.

Studies by various observers on muscular dystrophy, which occurs as a result of Vitamin E deficiency in rabbits and cattle, have shown instances of cardiac failure and changes in the heart muscle, although the results have not been constant. Monkeys maintained for years on E deficient diets showed no abnormalities of the cardiac muscle at autopsy, although most skeletal and smooth muscle did show dystrophic changes. Experiments on rabbits indicate that functional impairment may have occurred before anatomical change, and some believe the vitamin plays a role in intracellular oxidation.

The difficulty of applying experimental and theoretical considerations is due to: (1) the impossibility of demonstrating a constant cardiac lesion; (2) lack of knowledge of the function of the vitamin; and (3) unlikelihood of Vitamin E deficiency existing in man.

The experience of Vogelsang and Shute with an elderly male patient, who was being treated for thrombocytopenic purpura with Vitamin E and had coincidental improvement of angina pectoris, led these authors to use it in a variety of heart diseases, including a series of 84 patients with angina pectoris. Eighty-one showed improvement.

The present study represents an attempt to evaluate Vitamin E therapy on a small carefully controlled group of patients with angina pectoris. A two-step test similar to that described by Riseman and Stern was used, with careful control of such variables as room temperature, speed of testing and coincidental use of nitroglycerin. Base lines were obtained by three observations prior to therapy. The patients were then given 500 mg. of mixed tocopherols (equivalent to 250 mg. of alpha tocopherols) per day and performance tested at two or three weekly intervals. Patients were not permitted to use cod liver oil, mineral oil or iron preparations.

Eleven patients were accepted for the study, each of whom received a careful history, physical examination, blood and urine examinations, electrocardiogram and seven-foot heart x-ray. Each patient had had angina pectoris for a period which varied from one to ten years. The etiology of their heart disease was arteriosclerotic, or hypertensive and arteriosclerotic in 10 cases, syphilitic in one. The period over which the drug was taken varied from 4 weeks (in 2 cases) to 24 weeks (in 3 cases), the average for the group being 14 weeks. (1) results of two-step tests after therapy, (2) tabulation of the number of nitroglycerin tablets used, and (3) subjective feeling of improvement revealed that in no case was there either subjective or objective improvement in exercise tolerance following intensive treatment with tocopherols. 12 references. 1 table.—*Author's abstract.*

Thirty Years of Personal Observation of Angina Pectoris *(L'angine de poitrine d'après trente ans des observations personelles.) P. Halbron, Paris, France.* Bull. Acad. nat méd. 132: 525-28, Oct. 12, 1948.

In spite of the vast information provided by study of electro-cardiographic changes, by the surgical interruption of sympathetic fibers and other recent procedures the clinical study of anginal pain is believed still to have its place. A survey of 200 cases of this disorder is reported here.

It is pointed out that the clinical picture of precordial pain with varying radiation, accompanied by anxiety, and promptly relieved by vasodilators like the nitrites, is highly typical and commonly differentiates true angina from other less specific symptom complexes. The present series indicates that 75% of the cases occurred in men, as is generally the case, and that the time of survival after the onset of symptoms could not readily be predicted, some patients surviving for twenty years.

The age of onset likewise varied a great deal, the extremes being a young man of 29 with rheumatic aortic valve disease, and a man of 76. However, onset before the age of 40 was rare (less than 4%), while 58% of all cases started between the ages of 40 and 60, and an additional 18.5% between the ages of 60 and 70.

Pathologically, there was a high degree of correlation between aortic lesions and the occurrence of angina pectoris, but in only very few patients was there a significant degree of nephrosclerosis. In almost 10% there was evidence of cerebral vascular accidents, but peripheral arterial disease was very rare.

The clinical characteristics of the pain starting with effort are highly typical. Cold frequently precipitates it in very definite fashion, and pain with slight effort after meals is often an early diagnostic sign. The radiation of the pain down the left arm is almost uniform, occasionally also up into the neck, to the jaw or to the back. Atypical radiations were encountered: In 5 cases they were uniformly and only present in the right arm, in 5 others only in the back. In 6 cases the only pain appeared in the arms, without any chest pain at all. Some of these were treated for neuritis for varying periods of time, until the appearance of myocardial infarction. Another uncommon form of vascular symptoms is the primary syncope occurring on effort as the first symptom of anginal difficulties, and accompanied later by typical pain.

Digestive difficulties occur rather commonly, suggesting a chronic ulcer or duodenitis and often treated as such. The intensity of these symptoms is usually much less than those masking myocardial infarction. The association of anginal pain with cardiac decompensation was exceedingly rare, occurring in only 1% of the cases.

The etiology of the anginal attacks was attributed to aortic and coronary arteriosclerosis in about 60% of the cases. Syphilis was definitely responsible in less than 10%. The role of tobacco was definite: 9% of this series were heavy smokers who improved greatly when tobacco was withdrawn.

Since angina occurs so frequently in individuals with arteriosclerosis, one might postulate that it should be common among diabetics. However, only 2% of the cases of angina in this series were known diabetics. Rheumatic fever lesions with known valvular deformities were quite rare (2.5%), and other infectious diseases (e.g., malaria) played no role at all.

Endocrine disturbances appear to be of some importance especially in women: onset soon after menopause was a distinct impression. A distinct familial tendency was observed in the present series, so that a hereditary predisposition might be considered.

Office Diagnosis of Peripheral Vascular Insufficiency. *Walter Redisch, New York University School of Medicine, New York, N. Y.* J. M. Soc. New Jersey 46: 4-9, Jan. 1949.

In the office diagnosis of peripheral vascular disease, it is essential that a good history be obtained, including information concerning the use of tobacco and alcohol, the occupation, and the use of drugs, as well as all available data on the onset and nature of the symptoms and how they are affected by various factors, especially rest and exercise. The history of other diseases that affect the development of peripheral vascular disease is also of importance, particularly diabetes mellitus. Examination of the heart and lungs, taking of blood pressure, urinalysis and a complete blood count are a part of the routine examination. In the diagnosis of peripheral vascular disease, examination of the extremities is of chief importance. On the first inspection of the extremities the type of edema is noted; areas of pigmentation, signs of healed ulcers, presence of fresh ulcers, and, toward the distal end of the extremities, blebs, rosy spots and scaling are examined. If fresh ulcers are present, their size and the presence or absence of granulations are recorded. The condition of the skin is noted, and any evidence of beginning tissue necrosis is looked for. Varicosities of superficial veins are looked for with the extremity at rest. The next step in the examination is palpation of the brachial and radial arteries on the upper extremity and of the femoral, popliteal, dorsalis pedis and posterior tibial arteries on the lower extremity. Comparison between the extremities on the two sides is essential. If an extremity has been amputated, it is important to determine the reason for the amputation. If a coil of veins has accumulated in one place, this coil is palpated; if a thrill is felt and if the skin is warmer than in surrounding areas, this indicates an arteriovenous fistula; a bruit will usually be heard on auscultation. Deep palpation is done to determine whether cords are present, representing old organized thrombophlebitis; short superficial cords are sequelae of superficial thrombophlebitis in Buerger's disease. Palpation of peripheral arteries is also done for rigidity and tortuosity which indicate generalized arteriosclerosis. All these examinations are done with the extremities at rest.

Then changes produced by changing the position of the extremities—raising, lowering and movement—are studied. Venous return time may be studied with the use of a flat rubber band (a tourniquet, if not too thin, can

be used). This band is applied around the leg just below the band so as to obstruct venous but not arterial reflux; before the band is applied a small superficial vein on the dorsum of the foot which can be easily seen is emptied. The limb is then lowered and the obstructing band released, and the time in which the superficial vein refills noted; a refilling time over twenty seconds indicates arterial insufficiency. Intermittent claudication may be tested by observing the effect of measured work performance, such as a walk of a certain distance. The degree of arterial spasm, as compared with permanent changes, may be determined by studying the reflex vasodilatation by heat. This is only a crude test without a temperature-controlled room and a skin thermometry apparatus. For the test the lower extremities are exposed to the room temperature for thirty minutes; then both upper extremities are immersed in water of 43° to 45° C. (109° F.) for an hour; the temperature of the lower extremities in a room kept at 20° to 23° (41° F.) will rise; the more the temperature and color of the lower extremities improve, the more spasm is being released.

For the examination of the venous system, Homan's sign for deep thrombophlebitis—pain and rigidity in the calf on retroflexion of the foot with the leg held down is of value. There are many tests for competency of veins in varicosities; the Brodie-Trendelenburg test is done by digitally occluding the greater saphenous vein where it enters Rosenmueller's groove; or the modification of the Perthes test by Ochsner and Mahorner may be employed. For this test a tourniquet is applied around the upper thigh, and the patient is directed to walk around briskly; the effect on the varices is observed; then the test is repeated, once with the tourniquet around the middle of the thigh and once with it just below the knee. Pratt's method for testing the incompetency of the communicating branches by using an Ace bandage in addition to the tourniquet, may also be employed. A classification of the disorders of the vascular system is presented. While diagnosis of definite clinical entities can sometimes be made by office procedures, often a hospital circulation laboratory is necessary for exact diagnosis.

Roentgen Examination of the Soft Tissue in Acute Thrombosis. *J. Frimann-Dahl, Oslo Municipal Hospital, Ulleval, Norway.* Acta Radiol. 30: 1-8, Aug. 31, 1948.

Venography in the lower extremities with very early or beginning venous thrombosis often permits the definite demonstration of the characteristics of thrombus formation: irregular defects and discontinuities in the venous network. In view of the desirability of starting anticoagulant therapy as promptly as possible and of its small but definite dangers, conclusive demonstration of very early venous thrombosis is essential. Venography is expensive and often yields definite results only after the clinical picture has become clear cut.

Another roentgenologic approach to this problem is the examination of the soft tissue in early thrombosis of the lower extremities. Normally the subcutis is seen as a clear zone representing subcutaneous fat bordered on

the surface by a sharp line, the cutis-line, corresponding to the skin. The edge of the muscular tissue is likewise sharply defined normally. In the subcutis some veins and lymphatic vessels are seen rather faintly.

For the best pictures the patient is placed on a Bucky table, but adequate examination can be performed while he is lying in bed. The usual conditions of exposure are 40 to 50 kv. and 100 Ma., target-film distance 90 to 100 cm., exposure time 1/2 second. Film size must be planned to permit including the lower thigh in the film and to have the opposite side available for comparison.

Diagnosis is easier when the subcutaneous fat is well developed as in women, and more difficult with over-developed musculature. The diagnostic roentgenologic signs are: (1) thickening of the cutisline; (2) increased breadth of the subcutaneous fatty layer; (3) abnormal net-work designs in the subcutis; (4) increased density of the muscular shadow and blurring of its border. All these signs indicate edema. In 34 patients the x-ray diagnosis was often positive when the clinical findings were still indefinite. 6 references.

Incipient Symmetrical Peripheral Gangrene Complicating Paroxysmal Tachycardia. *D. Gordon Abrahams.* Brit. Heart J. 10: 191-94, July 1948.

A case of incipient symmetrical peripheral gangrene in a forty-seven year old woman is described, associated with extreme heart failure produced by persistent ventricular tachycardia. The patient was admitted complaining of faintness and a fluttering feeling around the heart. The pulse was fast. In the previous six weeks there had been two attacks, beginning with loss of consciousness, after which her extremities were very cold, cyanosed, and painful. The systolic pressure was 65 mm. in the arms, and 85 mm. in the legs, and the diastolic pressure was unobtainable. The heart was enlarged, and an apical thrill and murmur were noted. The neck veins were distended, while the arm veins appeared empty of blood. The liver was just palpable, and there were a few moist sounds at the lung bases. An electrocardiogram showed a regular paroxysmal ventricular tachycardia of 230 per minute. The tachycardia had precipitated an extreme circulatory failure. The patient died four hours after her admission despite treatment with quinidine.

At autopsy there was extensive syphilitic aortitis, with anuerysmal dilatation of the ascending part and the arch of the aorta. The muscle of the right ventricle and also the interventricular septum showed diffuse fibrotic infiltration. There were many large, discrete, granulomatous lesions over the internal surface of the right ventricle. The pulmonary artery was similarly affected. The diffuse infiltration and the granulomatous masses were syphilitic.

The case presents several points of interest. Gumma of the heart is comparatively rare. A paroxysm of ventricular tachycardia usually persists not more than one hour, but in the present case it lasted over three days. Neither arterial emboli nor syphilitic arteritis played any local part in the

genesis of the incipient gangrene; it seems certain that reflex peripheral vasospasm was responsible, and this was elicited by a critically low cardiac output in turn caused by persistent tachycardia. 11 references. 6 figures.

Peripheral Vascular Disease in the Lungs. *Robert P. Barden and David A. Cooper, Hospital of the University of Pennsylvania, Philadelphia.* Am. J. Roentgenol. 61: 17-22, Jan. 1949.

Vascular disease in the lungs may produce characteristic shadow patterns differing from those accompanying disease of the lymphatic or alveolar pulmonary structures. Five illustrative case histories are presented. Congestive lesions are illustrated by Case 1, a 50 year old female with pulmonary hemangioma. She complained of cyanosis and chronic cough with occasional hemoptysis for many years. Multiple subcutaneous hemangiomas were especially prominent over the dorsum of each hand. Serial roentgenograms of the chest showed unchanging nodular shadows through both lower lung fields possibly representing pulmonary hemangiomas. Roentgenoscopy might have been used to show pulsation of the nodules and decrease in their size with forced expiration against a closed glottis.

Intrinsic obstruction of pulmonary vessels is illustrated by Case 2, a 52 year old female with leukemia. She had enlarged lymph nodes, subcutaneous nodules, anemia, and purpura of two years' duration. A bone marrow smear showed myeloid leukemia. Roentgenograms of the chest showed many nodular shadows in the lower half of each lung and a pleural reaction at the bases. The shadows disappeared with roentgen therapy. The lesions may have been caused by leukemic thromboses of pulmonary vessels.

Carcinoma is illustrated in Case 3, a 39 year old male. He complained of cough, dyspnea, weakness, and anemia for four years. The sputum was positive for Monilia. Serial roentgenograms showed diffuse linear and nodular lung shadows, becoming progressively confluent. Autopsy showed carcinoma of the bile ducts with emboli.

Intrinsic disease of vessels is illustrated in Case 4, a 25 year old male. He had acute rheumatic fever. Roentgenograms at the height of the illness showed a diffuse hazy shadow obscuring the upper half of each lung without evidence of cardiac failure. Films after recovery showed an unchanging pattern of diffuse, symmetrical nodulation, possibly indicating areas of perivascular exudation. Blood vessels may also be obliterated by virtue of adjacent disease; many pneumonias produce vascular occlusion. When attention is centered on pulmonary consolidation, vascular damage is often overlooked.

Hypersensitivity states are illustrated in Case 5, a 45 year old male with periarteritis nodosa. He had rapid loss of weight, severe pains in all extremities, asthenia, and asthmatic attacks. He had gallstones and a basal metabolic rate of + 50. He had several attacks of respiratory embarrassment with cyanosis. These patients all had asthmatic attacks which were probably episodes of pulmonary edema, progressively severe, ending in respiratory failure. 10 references. 1 table. 5 figures.

6. Genitourinary Disorders and Diseases

Chronic Renal Insufficiency with Secondary Hyperparathyroidism. *A. Elkeles.* Proc. Roy. Soc. Med. 41: 658-60, Oct. 1948.

The case is presented of a 24 year old woman who had become increasingly pale and breathless during the previous two years, had lost approximately 28 lb. in weight, and had developed amenorrhea and irritation of the skin in the axillae, cubital fossae, under the breasts, in the groins and anogenital region and upper thighs. Physical examination showed her to be quite ill, apathetic and drowsy. The skin showed red-brown, isolated papules, linear lesions and almost black indurated areas. Blood pressure was 120/65. Blood examination showed hypochromic anemia with hemoglobin of 46% and R.B.C. 2,630,000. The urine showed albumin + 1 and no sugar. Blood calcium was 9.8 mg.%; plasma phosphorus 8.4 mg.%; plasma phosphatase 17.2%; total plasma proteins 6.17%; fibrin 0.6%; albumin 2.94; globulin 2.63; blood urea 304 mg.%. Roentgenograms showed a generalized osteoporosis; cortical thinning, especially of the long bones; and disintegration in the phalanges and os pubis. There were extensive calcifications in the subcutaneous tissues and extensive arteriosclerosis of the hands and feet. The patient died three months later, and autopsy showed chronic nephritis and marked parathyroid enlargement.

The differential diagnosis is sometimes difficult between primary and secondary hyperparathyroidism in a case of renal insufficiency. Renal damage in the primary form may follow precipitation of calcium in the renal pelves with resulting calculus formation and pyelonephritis, or calcium deposits in the renal parenchyma. These calcifications are usually recognizable on an x-ray and are an important diagnostic sign of primary hyperparathyroidism. The characteristic bone changes of osteitis fibrosa cystica are usually found, and there is usually increased serum calcium and low phosphorus in the blood.

This patient had characteristic primary renal insufficiency followed by secondary hyperparathyroidism. There were no metastatic renal calcium deposits, however, and the bony changes were not characteristic of osteitis fibrosa cystica. 2 references. 2 figures.

Can Vascular Shunting Be Induced In The Kidneys by Vasoactive Drugs? *François C. Reubi and Henry A. Schroeder, Washington University School of Medicine, and Barnes Hospital, St. Louis, Mo.* J. Clin. Investigation 28: 114-23, Jan. 1949.

Determinations of sodium para-amino hippurate (PAH) mannitol, oxygen content and hematocrit in renal venous and peripheral (or renal) arterial blood before and after injection of epinephrine, histamine or

pentothal were carried out in patients, 6 of whom were normotensive and 8 hypertensive. Determinations were also done in 15 dogs. Renal venous blood in patients was obtained by catheterization of the right renal vein.

There was an 11.4% maximal decrease in the extraction of PAH from the kidneys of patients after subcutaneous injection of epinephrine or histamine; results were inconclusive in dogs. Arteriovenous oxygen differences in 2 patients were increased by epinephrine; they were decreased in 3 patients.

There was a consistent difference in dogs in the oxygen capacity, hematocrit, and plasma protein content between renal arterial and renal venous blood; the latter was more concentrated. Epinephrine increased this difference. This loss of fluid from the renal blood may possibly have occurred through renal lymph vessels or other vascular channels by-passing the renal vein.

It is concluded that large intermittent renal shunts are not elicited in man by physiologic doses, or in dogs by larger doses, of epinephrine. Even in patients with essential hypertension, histamine or epinephrine caused relatively small and inconsistent changes ascribable to the presence of shunts. 27 references. 3 tables. 3 figures.

Fatal Renal Failure Following Transfusion of Compatible Blood and Excessive Intravenous Administration of Fluids. *M. Gerundo, Honolulu, Hawaii.* Hawaii M. J. 8: 184-87, Jan.-Feb. 1949.

This study covers a certain type of complication which may follow blood transfusions. The cases reported developed drowsiness, mental confusion, rising temperature and leukocytosis and oliguria, albuminuria and cylindruria. At the autopsy all presented the same picture; anasarca, pulmonary edema, and edema and congestion of kidneys. The latter showed definite signs of previous impairment of sclerosis.

Case No. 1, a laborer, was admitted to the hospital because of partial bowel obstruction. The urine showed a trace of albumin and a few red cells in the sediment. Following blood transfusions and a large amount of fluids intravenously, the urine showed 4 + albumin and granular casts. The patient was treated with further intravenous fluids and blood transfusions and succumbed with signs of pulmonary edema.

Case No. 2 was a 54 year old man admitted with the diagnosis of carcinoma of the rectum. Urinalysis showed albumin and granular casts. Following several blood transfusions, he became gradually worse, developed a fever and mental confusion, and died immediately following the operation.

Case No. 3 was a 56 year old man admitted to the hospital complaining of general weakness, soreness of the joints and swelling of the left knee. Urinalysis showed 3 + albumin, numerous casts and blood cells in the sediment. Following the blood transfusion he developed mental confusion and tremor of the hands. He was treated with further blood transfusions, but his condition became acutely worse.

Case No. 4, a 36 year old man was admitted and operated on for acute appendicitis. He complained of great difficulty in voiding and his urine contained albumin but no cast. During the postoperative course he received several blood transfusions and a large amount of fluids. Following the first blood transfusion he developed fever and leukocytis. His urine showed 4 + albumin and numerous casts. The patient died the eighth day following admission to the hospital.

In all 4 cases, the kidneys showed various stages of degeneration of the glomeruli, sclerosis, edema of the tubules and pigment masses or cellular casts in the lumina of the collecting tubules.

A simple procedure to avoid the danger of transfusion and excessive intravenous administration of fluids is to make repeated examinations of urine before and after transfusion. A heavy trace appearing and persisting after a blood transfusion should serve as a warning. Observation of mental alertness, turgor of the skin and changes in weight should be considered. Hematocrit values plus proteins, red cell count and hemoglobin determination are laboratory procedures to be carried out.

It appears evident that patients with renal impairment will get worse if given blood transfusions or intravenous fluids. 16 references.—*Author's abstract.*

(The transfusion of blood in moderate amount should not be withheld arbitrarily in patients for whom it is definitely indicated. The administration of excessive quantities of any fluid, however, is dangerous and harmful in cases of severe renal disease with oliguria.—ED.)

Treatment of Acute Uncomplicated Gonococcal Urethritis with a Single Dose Water-Soluble Penicillin Preparation. *Leo Loewe, Theodore Rosenthal, William Leifer, Perry Katzen, Harold B. Eiber and Sidney Cohen, Jewish Hospital, Brooklyn, N. Y.* J. Urol. 60: 958-63, Dec. 1948.

A new, single dose, dehydrated penicillin gelatin-dextrose mixture is effective for the routine treatment of acute, uncomplicated genococcic urethritis. It is water-soluble, non-toxic, non-irritant, non-allergenic and easy to administer by intramuscular or subcutaneous injection. Of the 128 patients suitable for statistical study, 123 (96.1% were satisfactorily "cured' and 2 (1.5%) were probably reinfections. Twenty-six of the infecting organisms in this series were examined for penicillin sensitivity. The values were unexpectedly high, ranging from 0.004-0.25 Oxford units per cc. of test broth for bacteriostasis, and 0.008-0.5 Oxford units per cc. of test broth for the minimal lethal dose. No correlation was found between penicillin sensitivity and failure of treatment. The percentage of successes in this series may be attributed to the concentration and duration of penicillin levels in the blood. The peak levels which persisted for 8 to 12 hours were sufficient to provide the minimal lethal dose for even the most resistant strains

of organisms encountered in this series. These results compare favorably with any previous studies conducted in a comparable manner. 3 tables.—*Author's abstract.*

Extrarenal Azotemia. Report of a Severe Case with Recovery. *Charles F. Appel and James H. Townsend, Mt. Auburn Hospital, Cambridge, Mass.* New England J. Med. 240: 95-97, Jan. 20, 1949.

The characteristic picture of extrarenal azotemia is that of renal failure without actual renal disease or renal disease not sufficient to explain the signs of renal failure present. In the mechanism of extrarenal azotemia Jeghers and Bakst consider these factors: drop in blood pressure, hypochloremia and hyponatremia, dehydration, liver damage, and protein catabolism. Fishberg considers a similar group of factors: hypochloremia, low arterial pressure, toxic nephritis and alkalosis. The common denominator of the significant factors in either group appears to be diminished blood flow through the glomeruli.

CASE REPORT

J. D., a 37 year old rubber factory worker developed headaches, vomiting and epigastric pain. He became severely dehydrated, oliguric, and was treated at home for peptic ulcer for two weeks. On admission to the hospital the blood non-protein nitrogen was found to be 200 mg.%, the blood chloride, 72 mEq. per l., and the CO combining power, 32.6 mEq. per l. After ten days of intensive electrolytic and hydrotherapy (primarily by mouth) the blood non-protein nitrogen fell to 42.5 mg.% and the blood chloride rose to 106 mEq. per. The blood pressure remained constant at 134 systolic, 84 diastolic. The subsequent return of renal function to normal was shown by an excretion of 60% of phenolsulfonphthalein in two hours (compared with 20% earlier in the hospitalization) and by the excretion of dye in the intravenous pyelogram four weeks after onset of illness. The sustained normal non-protein nitrogen of the blood for eight months and specific gravity of the urine of 1.025 and 1.020 two and four months after onset of illness helped to substantiate the return of renal function to normal.

The rationale in therapy of this case pererenal azotemia, which was preceded by dehydration and moderate intake of alkalis, was to restore the continual loss of fluids and electrolytes as soon as possible. In this way, hemoconcentration and dehydration were reduced, blood flow through the glomeruli increased, and normal renal excretion restored. 16 references. 1 figure.—*Author's abstract.*

On Tomography as an Adjunct to Urography. *P. T. Andersen, Roentgen Clinic, Central Hospital for Frederiksborg County, Hillerod, Denmark.* Acta Radio. 30: 225-236, Sept. 30, 1948.

Tomography has long established its value in the diagnosis of pulmonary disease but has been relatively little used elsewhere. The method, however, is quite applicable to other fields.

Because of the location of the kidneys close up against the muscles of the posterior wall of the abdomen, on a level with lower thoracic and upper lumbar vertebrae, the ordinary roentgenograms are often obscured by gas-filled loops of bowel or accumulations of feces. The outline of the kidneys is thus often blurred and diagnosis made difficult. Often it is also not possible to obtain satisfactory bowel preparation, with removal of gas and fecal masses. In some acute injuries no preparation at all may be possible.

In view of these considerations, tomography has been practiced on all patients as an addition to urographic examinations. The technic used is described in detail, and a number of case reports are submitted showing the obvious advantages of tomography of the kidneys.

It is suggested that tomography of the kidney regions be included as a routine procedure in all cases where there is much gas in the intestine, or where proper preparation is not possible; in out patients who can be spared additional loss of working time if they do not have to return for re-examination; in cases of prostatic hypertrophy and marked flatulence; and finally, in all instances where the urograms were unsatisfactory previously.

Pregnancy Complicated by Primary Torsion of a Normal Fallopian Tube. *C. L. Riley, Winchester, Va.* Virginia M. Monthly 76: 127, March 1949.

Primary torsion of a normal fallopian tube has been reported, but a survey of the literature indicates that primary torsion of a normal tube accompanying advanced pregnancy is a rare entity.

In the case reported the diagnosis was not made before operation, and, although an ovarian cyst with a twisted pedicle was considered, the absence of a palpable mass above and a negative pelvic examination did not lend support to this diagnosis.

CASE REPORT

W. F., age 24, was admitted to the hospital because of pregnancy (7 months) complicated by pain in the right lower quadrant of the abdomen. The pregnancy had been normal and uneventful until thirty-six hours before admission when she began to have persistent pain in the right lower quadrant. The pain was described as being constant but of moderate severity until twelve hours prior to admission when it became quite acute and was not relieved by hypodermic medication. There were no symptoms suggesting premature separation of the placenta, renal complications, etc.

Physical examination at the time of admission revealed a well developed and well nourished white female, unable to lie quietly because of excruciating pain in the right lower quadrant of the abdomen. T. 99, P. 90, R. 20. Examination of the abdomen revealed a normal pregnancy of seven months duration, acute tenderness and spasm of the right lower quadrant of the abdomen and no induration or swelling. Other physical findings were within normal limits and pelvic examination was negative. B.P. 110/80.

Laboratory findings: RBC-3,640,000; WBC-11,050; Hbg. 72%; Polys-81; Lymphs-19; Eagle-negative. Urinalysis—Amber, acid, 1.014, hazy, albumin: trace, sugar: negative, 6-8 WBC per HPF.

Operation revealed the right fallopian tube to be twisted, gangrenous, and distended with serosanguineous fluid. The ovary and appendix were grossly normal. Operation consisted of a right salpingectomy. The ovary and appendix were not disturbed. The patient made an uneventful recovery and was discharged from the hospital on the tenth post-operative day. She was delivered normally of a living child at term.

SUMMARY

Primary torsion of a normal Fallopian tube occurring during advanced pregnancy with accompanying alarming symptoms has been presented. Convalescence following removal of a gangrenous tube was uneventful and the patient progressed normally to term and was delivered normally at that time. The appendix was not removed, as it was believed that a minimal amount of operative intervention would be less likely to precipitate premature labor. 1 reference.—*Author's abstract.*

Sodium Hyposulfite Clearance Test as a Measure of Glomerular Filtration. *(Le test de l'hyposulfite de sodium pour la mesure de la filtration glomérulaire). L. Langeron, M. Paget, N. Nolf and J. Duriez, Biochemical Laboratory and Medical Clinic, School of Medicine, University of Lille, France.* Presse méd. 57: 222-223, March 12, 1949.

Rehberg introduced in 1926 the creatinine clearance test as an index of glomerular filtration, on the assumption that creatinine was solely filtered through the glomeruli and not reabsorbed in the tubules. Later studies indicated, however, that in comparison with inulin, creatinine was both filtered through glomeruli and secreted by tubules, and therefore did not give a true picture of glomerular filtration.

In France inulin is often not obtainable, and the different lots of inulin may vary widely in physical characteristics, particularly molecular weight. Consequently sodium hyposulfite was decided upon to serve as substitute. Previous work had indicated that this substance was filtered through glomeruli but neither excreted nor absorbed by the tubules.

The sodium hyposulfite clearance test is based on the same principle as other renal clearance tests, namely the concentration index, the relationship between urinary and plasma concentration at a given time as a function of urine output. The hyposulfite must be administered intravenously in doses of 0.2 Gm. per Kg. body weight as a ten per cent solution. Following injection there is a period of 20 to 30 minutes during which the substance is distributed throughout body tissues and its equilibrium in the plasma

established. Subsequently the plasma concentration falls steadily and excretion lasts for about 2 hours. In the urine 60 to 70% of the amount of hyposulfite injected can be removed. The loss of the remainder can probably be ascribed to oxidation processes.

In practice the test is performed as follows: The bladder is emptied and then immediately 100 - 150 cc. of a warmed 10% solution of sodium hyposulfite injected in a period of ten minutes (0.2 g/kg). If the solution is administered slowly unpleasant effects are practically never observed. Thirty and fifty minutes after end of the injection, urine is collected, and samples of blood obtained. The urine volume is determined accurately.

Clearance is calculated according to the formula: $C = \frac{U \times V}{P}$ where U = concentration in the urine, P = concentration in the plasma and V = the volume of urine excreted per minute.

The results of clearance tests closely approximated those of the inulin procedure. In normal persons the clearances were always between 110 and 150 cc. per minute, commonly 115 to 125 cc. / min. which compares well with the normal inulin clearance of 120 cc. / min.

In individuals with chronic glomerulonephritis, markedly reduced kidney function, but no hypertension, the clearance rates varied between 12 to 20 cc. / min. indicating markedly diminished glomerular filtration. In essential hypertension or malignant renal hypertension the clearance rates are a function of the degree of renal involvement. In essential hypertension glomerular filtration may be normal or even increased. Similarly, in patients with cardiac decompensation but adequate renal function the clearance was close to normal.

It is concluded that the clearance test performed with sodium hyposulfite is equal to that performed with inulin and can be a valuable adjunct to diagnostic procedure. 8 references.

Endarteriectomy to Remove the Block Causing Gangrene in Diabetic Arteritis. *(L'endartériectomie désobliterante dans le traitement de la gangrène diabétique artéritique). R. Boulin, P. Uhry and Nogrette, Paris, France.* Progrès méd. 77: 3-8, Jan. 10, 1949.

With the advent of chemotherapy and of methods for the prompt and adequate control of diabetes the prognosis of diabetic gangrene has been much improved. Treatment with vasodilators directed against ischemia has contributed to the satisfactory management. Nevertheless, amputation is often necessary when large arterial trunks are blocked. The method proposed, and used successfully in a few cases consists of the surgical removal of the blocking tissue inside the larger arterial trunks with resulting continuity of blood flow and removal of ischemia.

The method was first devised and tried by the Spanish surgeon J. Cid dos Santos in 5 cases. Essentially, the steps consisted of the following: (1) preoperative arteriography with exact localization of the arterial block;

(2) short incisions above and below the blocked area after proper exposure of the vessel; (3) heparinization during and after the operation; (4) curettage of the blocked segment between the two incisions with special instruments; (5) suture of the two incisions; (6) postoperative arteriography.

The method was soon modified in order to permit more adequate and simpler removal of the blocking tissues. Instead of two incisions and curettage, the incision was extended over the entire length of the blocked vessel and the blocking, diseased tissues were removed by sharp dissection. This permitted the removal of tissues down to the external elastic membrane whenever necessary. Additional care was then necessary for the long and difficult arterial suture. In several cases histological examination of the resected tissue indicated that it was completely necrotic. In some of the patients, successfully operated upon, and subsequently dying from other causes, histological examination revealed a unicellular layer of leukocytes, covering the exposed tissue of the new lumen, with endothelium growing back from the mouths of collaterals preserved in the operation, and from the ends of the operative site.

Two patients with uncontrolled diabetes are reported who developed diabetic arteritis in association with an injury, and subsequently showed a very painful obliterating arteritis with peripheral ischemia and beginning gangrene. Both were quckly treated with large amounts of insulin, fluids and electrolytes, and given adequate doses of penicillin. Subsequently, the arterial block was visualized by arteriography and found in one case in the femoral artery, in the other at the bifurcation of the aorta. Endarteriectomy was performed with the removal of necrotic tissues down to the external elastic membrane and reconstruction of the vessel. The peripheral pains persisted for several days postoperatively, then subsided while the patients continued on penicillin and heparin. There was no peripheral gangrene. No amputation was necessary. Post-operative arteriography three weeks after operation indicated satisfactory patency of the operated vessel, as did follow-up examinations six months later.

It is stressed that diabetic arteritis may have a relatively sudden onset, with intense pain leading quickly to ischemia. Neither of the two patients presented here was aware of his diabetes. Trauma as a precipitating cause of the arteritis appears to be frequent. After satisfactory course of the operation, strict regulation of the diabetes, and avoidance of trauma must be insisted upon. 7 references.

7. Gastrointestinal Disorders and Diseases

A Rapid Method of Roentgenologic Examination of the Small Intestine: a Preliminary Report. *Sydney Weintraub and Robert G. Williams, The New York Hospital, Cornell Medical Center, New York, N. Y.* Am. J. Roentgenol. 61: 45-55, Jan. 1949.

Roentgenoscopic and roentgenographic examination is made of the esophagus, stomach and duodenum, using 4 oz. of barium and 4 oz. of

normal saline at room temperature. The patient then drinks 8 oz. of ice cold normal saline, and a 14 by 17 inch abdominal film is taken after five minutes. He then drinks a second 8 oz. portion of ice cold normal saline, and the abdominal film is taken at fifteen minutes, and again at thirty minutes. All films are examined wet, and the roentgenologist roentgenoscopes and takes spot films of suspicious areas. If the head of the meal has reached the cecum, he may roentgenoscope and spot the terminal ileum; otherwise additional films are taken each half hour until the head of the meal reaches the cecum.

In 72 of 87 normal cases, the head of the meal reached the cecum in 1/2 hour or less; in 6 cases it took 1/2 to 1 hour; in 9 cases it took over 1 hour. The mucosal pattern was as good or better than that obtained on routine small intertinal examinations. In 42 cases barium entered the cecum in 5 to 15 minutes. In 10 of 17 pathological cases, the head of the meal reached the cecum in 1 hour or less. Five illustrative cases are presented.

In deficiency states or disordered motor function patterns and in sprue, there is marked delay in the passage of barium. The present method shows that this delay is only relative; in one case of sprue the meal reached the cecum in 150 minutes, whereas with the hourly method of study it would have taken 6 to 8 hours. Small intestine tumors are well demonstrated by the new method.

The basis of this method is the action of a cold solution in relaxing gastric tonus and opening the pylorus. 5 references. 3 tables. 5 figures.

Two Unusual Cases of Disease of the Alimentary Canal. *L. Hardy Wilson, Launceston, Tasmania.* M. J. Australia 36, pt. 1: 234-36, Feb. 19, 1949.

In the first case reported, the patient was a man 60 years of age who complained of dyspnea, and "dyspepsia" (anorexia, nausea and vomiting); he had lost weight in the last few months. Examination showed the lungs dull to percussion toward the bases posteriorly and massive ascites. No definite diagnosis was made, and after the patient had been in the hospital for eight weeks, operation was advised but refused. He died suddenly from pulmonary embolism thirteen weeks after admission. During that time parecentesis for the ascites was done seven times; the fluid withdrawn contained lymphocytes or large endothelial cells. At autopsy three separate tumors, 1 to 2 in. in diameter, were found in the small intestine, the distal tumor being the largest. Histologically, these tumors were lymphosarcoma. The liver was enlarged but showed no metastases. The glandular involvement was unusual in this case, as the mesenteric glands showed no macroscopic involvement, but glands about the diaphragm and one gland in the

supraclavicular region were enlarged. There was nothing found to explain the massive ascites, and the tumors in the small intestine were much too small to cause obstruction of the vena cava.

In the second case, the chief symptom was epigastric pain aggravated by food; the bowel movements had previously been regular, but recently constipation had developed. Roentgen-ray examination with the barium meal showed nothing abnormal in the stomach or duodenum, but the opaque meal did not pass the hepatic flexure. Two days after admission, jaundice and fever developed. Laparotomy was done on the twentieth day after admission. The colon was found to be normal, but the omentum and mesentery were swollen and indurated; the wall of the stomach was also indurated and thickened; an intramural abscess of the stomach wall was opened and drained. Penicillin and sulfadiazine were given, until culture of the pus from the abscess showed Friedländer's bacillus. Streptomycin was then given, and the temperature fell to normal, but the patient's general condition grew worse and he died on the eighteenth postoperative day. No autopsy was done. As far as could be ascertained no similar case of infection of the stomach wall and mesentery due to Friedländer's bacillus has been reported. Streptomycin which is effective against this organism in vitro failed to effect a cure in this case. 6 references.

DDT Poisoning and the Elusive "Virus X": A New Cause of Gastroenteritis. *Morton S. Biskind, New York, N. Y.* Am. J. Digest. Dis. 16: 79-84, March 1949.

The syndrome caused by the hypothetical "virus X" consists of acute afebrile gastrointestinal symptoms often accompanied by respiratory symptoms, a sense of constriction or lump in the throat, joint pains, muscular weakness and exhaustion. There may be headache, vertigo, syncope and various paresthesias. Severe apprehension is common. Irregular smooth muscle spasm of the gastrointestinal tract may persist for weeks after the acute symptoms subside. The syndrome is especially characterized by persistence of some symptoms, repeated recurrence of others for months, and lack of apparent causes for the severe subjective symptoms.

DDT was soon seriously considered as a possible cause because the virus X epidemic first developed coincidently with widespread use of DDT among the general population. Man and other mammals were supposedly protected from poisoning by the fact that its solubility is restricted to lipoids and lipoid solvents. The symptoms of clinical poisoning by DDT are quite similar to those of virus X. DDT has been extensively used both outdoors and indoors, in restaurants and homes. Sprays are inhaled and skin, bedding, textiles, food and food utensils extensively contaminated. Animals are extensively dusted and large areas sprayed with it for mosquito control. It accumulates in the fat and appears in the milk of animals that feed on pastures or fodder sprayed with it. Cooking does not affect DDT, and it is practically impossible to remove it completely from contaminated food.. It is slowly excreted

in the urine so that cumulative poisoning can and undoubtedly does occur. It has been demonstrated in the blood, bile, liver, kidney and central nervous system and may be chemically detected in muscles as long as five weeks after cessation of exposure.

DDT was extensively used by the armed services during the recent war, and the clinical syndrome above described frequently occurred but was attributed to other causes, usually endemic enteric infections. Investigations of 5 adult human male volunteers exposed to cutaneous absorption or ingestion of DDT solutions and inhalation of its aerosols showed that they developed symptoms similar to the virus X syndrome. Review of the literature showed at least 46 reported cases of DDT poisoning in human beings. It is self-evident that a compound as lethal to insects, fish, birds and animals as DDT could not be nontoxic for human beings. It has previously been demonstrated that solutions exceeding 0.5% DDT were unsafe for human use, but American commercial preparations usually contain from 3 to 10% and are available for indiscriminate use. DDT solutions are constantly used with absolutely no precautions to avoid personal contact. Yet several cases of fatal illness were found in exposed animals. Two dogs sprayed with DDT developed "distemper" and died; a dog in an apartment extensively sprayed with DDT developed convulsions and died in twenty-four hours, etc.

These investigations emphasize the warning issued by the U. S. Army and Public Health Service in 1945 against the indiscriminate use of DDT and indicate that the so-called virus X syndrome is actually DDT poisoning. 37 references.

Recent Concepts in the Treatment of Hepatic Disease. *Oscar D. Ratnoff, Johns Hopkins University School of Medicine, Baltimore, Md.* Bull. Johns Hopkins Hosp. 84: 101-115, Feb. 1949.

During the last dozen years the treatment of cirrhosis of the liver has undergone a radical change. This change has resulted in some improvement in the life expectancy of patients with cirrhosis, though not as much as one would like to see. Early in the twentieth century, experimental evidence began to appear which seemed to indicate that the ingestion of meat and of fat was harmful to patients with liver disease, whereas carbohydrates exerted a beneficial effect. In 1937, Patek reported results with a radical departure in therapy. He undertook to treat patients with cirrhosis with a diet rich in B vitamins, supplemented by oral and parenteral B vitamins. Ten of 13 patients fed a balanced diet of approximately 300 Gm. of carbohydrate, 100 Gm. of protein and 120 Gm. of fat showed striking improvement. Patek appreciated the fact that the value of the diet given these patients did not necessarily depend upon any single component, and in further studies an even higher caloric intake of protein, carbohydrate and fat was given. Thus, the dietetic regimen of patients under Patek's care now includes approximately 350 Gm. of carbohydrate, 140 Gm. of protein, and 175 Gm. of fat,

supplemented with 50 Gm. of powdered brewer's yeast or an oral B complex preparation. Intramuscular injection of thiamine chloride, 5 mg. daily, and unconcentrated liver extract, 5 cc. twice weekly, is given. With this regimen, about 45% of patients survived 2 years after the onset of ascites, compared with only 20% of patients treated between 1916 and 1938.

In recent years experimental evidence has appeared which seems to place the use of a highly nutritious regimen on a rational basis. Various investigators observed that animals fed diets relatively low in protein and relatively high in fat developed necrosis of liver cells, fatty infiltration of the liver and an increase in the fibrous tissue of the liver. Daft and his associates, and Himsworth, demonstrated that the factors responsible for the development of fatty infiltration of the liver and of hepatic necrosis were not identical.

Evidence of the experimental value of choline, methionine, and combinations of choline and methionine with cystine has led to the use of these substances as adjuvants to a highly nutritious diet in the treatment of cirrhosis. Suffice it to say their value under these conditions is unproved. Perhaps this is because any diversified nutritious diet is rich in the food necessary for the nutrition of the liver. Moreover, experimental diets deficient in these protective substances are achieved only with the greatest of care. For example, arguments for the use of liver fat diets are based upon experiments in which the composition of the diet is completely artificial. In practice, if the amount of fat in the diet is limited, the diet is usually so unpalatable that the patient fails to eat enough of anything.

Recently the use of intravenously administered liver extracts has been recommended for patients with Laennec's cirrhosis. Recent experience from the Rockefeller Institute and elsewhere has been most encouraging.

Diuretics such as mercurial compounds and ammonium chloride are important weapons in the treatment of ascites. Large doses of intravenously administered albumin, for example 100 Gm. a day, produce a diuresis but are not without danger. Paracentesis should be resorted to relatively early. Bleeding from the gastro-intestinal tract should be treated with rest and early transfusion with whole blood; food should be withheld until signs of active bleeding have disappeared.

Hoagland and his associates demonstrated that except for rest, therapy has little or no effect on the course of acute infectious hepatitis, nor did the administration of crude liver extract or methionine have any benefit. 79 references. 4 figures.—*Author's abstract.*

The Validity of Laboratory Evidence in the Diagnosis of the Sequelae of Acute Hepatitis. *Henry J. Tumen and Edwin M. Cohn, University of Pennsylvania and Jewish Hospital, Philadelphia, Pa.* Gastroenterology 12: 92-107, Jan. 1949.

Twenty-one patients, who had had acute hepatitis from six months to ten years previously, were studied by means of a group of laboratory procedures which included serum bilirubin determinations, examination of the urine for

urobilinogen, the bromsulfalein test, hippuric acid synthesis, determination of the serum cholesterol and of the prothrombin level, the cephalin cholesterol flocculation test, thymol turbidity and thymol flocculation tests, and colloidal gold reaction. Five of these patients had symptoms suggesting chronic active hepatitis, seven had hepatomegaly. The others had no clinical evidence of hepatic disease.

Some abnormality in the responses to one or more of these tests was noted in all of the patients. In 2 patients who were symptom-free, however, the only abnormality was very slight hypercholesterolemia, which may be considered to be of only questionable significance.

The hippuric acid synthesis test was not abnormal in any of the 18 patients in whom it was performed. The amount of urobilinogen in the urine was normal in 20 of the 21 patients studied. These two tests seemed relatively insensitive in detecting residual hepatic changes following hepatitis.

The various flocculation tests gave normal responses in all but 4 of the patients. The cephalin cholesterol flocculation was positive in 2 and the colloidal gold reaction was positive in 3. In only 2 patients were the flocculation tests strikingly abnormal. Although 1 of these 2 patients had clinical evidence of active liver disease, such evidence was much less pronounced in the other patient, so that in these 2 individuals no correlation between positive flocculations and the clinical features of hepatitis could be observed. In general, the flocculation tests were of little value in the recognition of residual liver dysfunction.

Hyperbilirubinemia was found in 14 of the 21 patients. This consisted of increase in only direct reacting bilirubin in 9 of the 14 patients. No instance of marked increase in the indirect reacting bilirubin was seen. The degree of hyperbilirubinemia was slight in most instances, but even this slight increase in bilirubin may have diagnostic significance and indicate definite hepatic dysfunction, since it was not encountered without other evidence of liver disturbance.

Some degree of excessive bromsulfalein retention was also encountered in 14 of the 21 patients studied. This was also usually of slight degree. Although found frequently, bromsulfalein retention was occasionally absent in the face of other evidence of hepatic dysfunction, so that a normal response to the bromsulfalein test may not be considered as excluding the presence of residual hepatic dysfunction following hepatitis.

In 8 of the 21 patients, a low prothrombin level was found. All 8 of these patients had abnormal responses to one or more of the other tests used, but in some instances the hypoprothrombinemia was the most striking laboratory evidence of hepatic disorder. Vitamin K was given to 5 of these 8 patients and the prothrombin level responded slowly or not at all to this therapy. The hypoprothrombinemia seems, therefore, to indicate that a specific liver dysfunction remained following acute hepatitis. The abnormality may exist even though other liver function tests are relatively normal.

Lowering of the cholesterol ester ratio was seen in only 1 patient and only 1 patient had decrease of the total cholesterol. Ten of the 21 patients had hypercholesterolemia. Although this finding need not indicate dysfunction of the liver, its demonstration in association with other laboratory evidence of hepatic disturbance following hepatitis calls for further investigation.

In this group of patients we could not find any close relation between the clinical features—symptoms and hepatomegaly—and the responses to the liver function tests used.

Patients who had had acute hepatitis not infrequently gave abnormal responses to various liver function tests. The degree of abnormality was often slight and not necessarily indicative of disease that was active clinically. The prognostic significance of such findings can be determined only by repeated studies. 23 references. 12 tables.—*Author's abstract.*

(Failure of such patients with hypoprothrombinemia to respond to the administration of a suitable preparation of Vitamin K usually indicates grave hepatic injury.—ED.*)*

Medical Therapy in Jaundice. *I. R. Jankelson, Tufts College Medical School and Leo R. Milner, Beth Israel Hospital, Boston, Mass.* Rev. Gastroenterol. 16: 130-41, Feb. 1949.

Jaundice is classified as (1) prehepatic, (2) hepatocellular and (3) posthepatic. Proper treatment of a jaundiced patient depends upon a definitive diagnosis. However, in many cases such diagnosis is impossible when the patient is first seen. In such instances, while the patient is observed clinically, he should be treated medically very much like a proven case of hepatocellular jaundice such as the authors describe.

In the treatment of prehepatic jaundice the underlying condition, namely hemolysis of whatever cause, is the focal point of attack. With the alleviation or cure of the underlying hemolysis the jaundice is relieved or cured.

Hepatocellular jaundice may be acute or chronic and includes infectious hepatitis, homologous serum hepatitis, acute or subacute yellow atrophy, toxic hepatitis, Weil's disease, amebic hepatitis, cirrhosis of the liver, syphilis of the liver and primary and secondary malignancy of the liver.

Infectious and homologous serum hepatitis and their treatment are described as examples of acute liver disease, and cirrhosis of the liver in the chronic diseases and special therapeutic considerations in the other diseases are mentioned, and preventive measures in these diseases are discussed.

The medical treatment of infectious or homologous serum hepatitis consists primarily of rest and proper diet. Complete bed rest should be enforced in the severer cases; relative rest in the milder cases may suffice. Early ambulation or early resumption of activities predisposes to recurrences and chronic hepatitis. Rest should be insisted upon until jaundice and liver tenderness disappear. The diet should consist of at least 350 Gm. of carbo-

hydrates, 75-125 Gm. of protein and 50-75 Gm. of fats. Fats, even in larger amounts, are not injurious and add to the palatability of the diet. Only if the patient cannot take an adequate diet per os, must one resort to parenteral alimentation with amino acids, glucose and saline. Antibiotics and sulfonamides are of no value, nor are methionine, choline and cystine of benefit in the acute cases. Multivitamins and crude liver are valuable adjuncts.

The treatment of cirrhosis of the liver is largely dietetic. The diet should be well balanced and contain 3,000 or more calories, and should include 350 or more Gm. of carbohydrates, 125-200 Gm. of protein and 50-75 Gm. of fats. Parenteral feedings are instituted where the patient cannot eat sufficient food. Amino acids, plasma, human albumin, and glucose are useful here. Liberal amounts of B complex vitamins are a major adjunct. Other vitamins should be given as indicated. Crude liver extract is valuable. Methionine, as well as choline and cystine are definitely lipotrophic amino acids and are of greatest value in fatty infiltration of the liver. Alcohol is definitely contraindicated. Persistent and prolonged treatment must be carried out.

Posthepatic jaundice is practically never an emergency, and proper medical treatment preoperatively reduces the risk of the operation. Postoperatively, the cooperation of the surgeon and clinician results in reduced mortality and diminished morbidity. Accidental diseases, such as cardiac or renal should be treated pre- and postoperatively in the usual manner. 37 references.—*Author's abstract.*

The Treatment of Peptic Ulcer with Injections of Serum Obtained During an Acute Attack. *(Le traitement des ulcères gastroduodénaux par le sérum prélevé au décours de la crise ulcéreuse). R. Carvaillo, Paris, France.* Presse méd. 57: 397, April 30, 1949.

It is frequently observed that acute attacks of peptic ulcer come and go with great abruptness and that they heal spontaneously very rapidly. Such cases, in the absence of any therapy, suggest a strong resemblance of the patient's reaction to immunity responses. On the basis of such a theoretical consideration, it was attempted to evaluate the possible curative action of serum obtained from individuals just recovered from an acute peptic ulcer. The serum was commonly obtained from five to fifteen days after the onset of the painful episode of an acute ulcer, and was commonly injected in amounts of 10 cc. subcutaneously into individuals suffering from an early attack of peptic ulcer.

This form of treatment was evaluated in 104 patients with respect to symptoms of the acute attack, radiological progress of the lesion, and duration of the periods of remission. The serum was injected as early as possible in the course of the acute attack, usually within the first 3 days. In about 30% of cases the acute attack was suddenly terminated by a single injection of serum, within 24 to 72 hours. In 39 other cases (40%) the symptoms subsided after a second injection of an equal amount of serum.

In 18 more patients the 2 injections failed to control pain, discomfort and objective signs of ulcer, but improvement followed if 3 to 5 injections were given. In 10 patients no beneficial effect followed the injection of serum. In 55% of cases radiological signs of ulcer disappeared within less than two weeks. Periods of remission between attacks appeared to be greatly lengthened.

Rapid Healing of Peptic Ulcers in Patients Receiving Fresh Cabbage Juice. *Garnett Cheney, Stanford University School of Medicine, San Francisco, Calif.* California Med. 70: 10-15 Jan. 1949.

Thirteen patients with peptic ulcer were treated with fresh cabbage juice, which, experiments have indicated, contains an anti-peptic ulcer factor. This factor (vitamin U) prevents the development of histamine-induced peptic ulcers in guinea pigs.

The average crater healing time for 7 of these patients who had duodenal ulcer was only 10.4 days, while the average time as reported in the literature, in 62 patients treated by standard therapy, was 37 days.

The average crater healing time for 6 patients with gastric ulcer treated with cabbage juice was only 7.3 days, compared with 42 days, as reported in the literature, for 6 patients treated by standard therapy.

The rapid healing of peptic ulcers observed radiologically and gastroscopically in 13 patients treated with fresh cabbage juice indicates that the anti-peptic ulcer dietary factor may play an important role in the genesis of peptic ulcer in man. 10 references. 1 table. 3 figures (2 graphs).—*Author's abstract.*

8. Blood and Lymphatic Disorders and Diseases

Bone Marrow Aspirations. *C. H. Peters and W. L. Larson, Bismarck, N. D.* Journal Lancet 69: 98-102, March 1949.

Bone marrow aspiration is indicated in obscure diseases of the blood and blood forming organs in which a diagnosis cannot be made by the usual methods. The authors use the method of Limarzi. In this, the area in the midline from the first to the fourth costal interspace anteriorly is prepared and a puncture site opposite the second interspace anesthetized down to the periosteum. A special, very strong 16 gauge needle is used. It should have a guard or flange to prevent its entering too deeply. The needle is inserted at an angle between 45° and 90° and pushed in until it enters the marrow cavity. The sensation on entry is usually similar to that felt on spinal puncture but, if it is not felt, aspiration must be done to determine whether or not the marrow cavity has been entered. The stylet is then removed, a 5 to 10 cc. syringe applied and 1 cc. of bone marrow aspirated. This usually causes a sharp momentary pain. Only a small amount of marrow is taken in order to have a roughly standardized procedure and to prevent excessive

dilution with sinusoidal blood. Some prefer to aspirate only 0.1 to 0.2 cc. of marrow. The aspirated material is immediately placed in small paraffin-lined Kahn tubes containing a small amount of powdered heparin. The material is well mixed and 1 cc. placed in a Wintrobe hematocrit tube with a pipette and centrifuged for five minutes at about 2000 R.P.M. The contents of the tube form into four distinct layers. Fat and most of the plasma are removed from the tube and a little of the remaining plasma mixed with the third or myeloiderythroid layer. Some of this material is then aspirated from the tube, placed on paraffin lined watch glasses and well mixed. Blood films are made from this and stained with Wright or May-Grünwald-Giemsa stain. This method is especially helpful in diagnosing pernicious anemia, acute leukemia, primary thrombocytopenic purpura, aplastic anemia, agranulocytosis, primary neutropenia and splenic panhematocytopenia, multiple myeloma, anemia of pregnancy, acute disseminated lupus erythematosus, kala-azar, Gaucher's disease and others of relative rarity. Bone marrow has also recently been aspirated from the vertebral spinous processes and the iliac crest. 5 references. 8 figures.

Chemotherapy in Leukemia, Hodgkin's Disease, and Allied Disorders. *J. Bichel, Radium Center for Jutland, Denmark.* Acta Radiol. 30: 49-63, Aug. 31, 1948.

Chemotherapy in Leukemia, Hodgkin's Disease, and Allied Disorders. different from the normal cells of the organism in many respects. Consequently it is possible to interfere with the vital processes of the micro-organisms without simultaneous harmful effect on the normal cells of the host.

Cancer cells in general also differ from the normal cells of the organisms in some fundamental ways, not fully defined, but their relationships to the host cells remain close. Consequently any agents that specifically injure cancer cells may similarly, though to a lesser extent, injure normal cells. To-date the search for any substance with selective destructive action on malignant cells has been unsuccessful. Most chemotherapeutic agents used today are based on the fact that malignant cells are evidently more susceptible to damage than normal cells. It is not certain whether this characteristic is a function of their more rapid proliferation.

The chemotherapeutic agents available at present are toxic substances which in small doses inhibit the rapidly proliferating malignant tissue but likewise affect other susceptible tissues and in larger doses (which might effectively destroy all malignant tissue) so damage normal tissues of the organism as to interfere with survival of the host. The rapidly proliferating cells of the blood forming organs are among the most easily damaged by the agents.

Urethane, the nitrogen mustards and stilbamidine are discussed from the standpoint of their chemistry and their biological actions. It is concluded that chemotherapeutic agents will have to be found, based on real qualitative, rather than only quantitative differences between their action on malignant and normal cells.

Hodgkin's Disease: a Histopathological and Clinical Classification with Radiotherapeutic Response. *Philip E. Sahyoun and Stuart J. Eisenberg, Medical College of Virginia, Richmond, Va.* Am. J. Roentgenol. 61: 369-79, March 1949.

The literature is reviewed relative to opinions concerning etiology and classification of Hodgkin's disease. Twenty-four cases were studied with the object of showing that careful evaluation of the histopathological picture is helpful in the prognosis of course and life expectancy. The histopathology and clinical course can be correlated.

Based on histopathological criteria and approximate range of maximum life expectancy, a classification of Hodgkin's disease is presented. There is a compactly cellular (slowly progressing) type, persisting 48 to 160 months. In this type, the architecture of the lymph node is altered and there are irregular proliferations of reticulo-endothelial cells with development of Sternberg-Reed cells. Pleomorphism is always present but not marked. The proliferation is chiefly of lymphoid and reticulo-endothelial nature with a compact structure. There is no marked fibrosis or necrosis. There are a few scattered eosinophiles and plasma cells. Eleven illustrative cases are described but only 7 were followed long enough to determine the course. Of these, 5 followed the histopathologically expected course, while 1 was more compatible with the acute and 1 with the fibrogranulomatous type.

A second type is fibrogranulomatous (moderately progressing), persisting 20 to 60 months. Six cases are described. There is a typical picture of Hodgkin's granuloma. There is proliferation of reticulo-endothelial cells, and Sternberg-Reed cells, and pleomorphism with abundance of eosinophils, plasma cells and other leukocytes. There is a tendency to fibrosis and necrosis. All 6 cases had a clinical course compatible with that of a fibrogranulomatous type of Hodgkin's disease.

A third type is loosely cellular (rapidly progressing), persisting 12 to 20 months. Seven cases are described. The architecture of the node is destroyed and replaced by loose reticulo-endothelial cells with primitive Sternberg-Reed cell formation. There is pleomorphism. There may be invasion of the capsule and of lymphatics and blood vessels. The tumor is highly vascular. Of 7 cases, 6 followed the expected course.

There is a correlation between histopathologically expected course and actual course. Of 19 cases adequately followed, the courses of 17 verified the histopathological prognostication. 27 references. 3 figures.

The Nitrogen Mustards in Hodgkin's Disease: Observations in 50 Cases. *(Les dérivés azotés de l'yperite dans la maladie de Hodgkin, d'après 50 observations.) Justin-Besançon, S. Lamotte-Barillon, and C. Polonovski, Paris, France.* Bull. Acad. nat. méd. 133: 148-52, Feb. 15, 1949.

Fifty cases of Hodgkin's disease were treated with methylbis-chlorethylamine and observed over a period of three years. The cases are reviewed and discussed under the heading of the results obtained.

In the majority of instances the results were gratifying, but not spectacular. The patients felt improved, the objective signs of the illness regressed and there was an increase of weight and strength. However, this remission lasted only for a few months. In a small number of cases the results could be called brilliant: all signs and symptoms disappeared and the patients returned to their work. Three cases of the present series had a complete remission lasting for at least three years during which they have been completely well, after a single course of nitrogen mustard administration.

Very poor results, with no regression of signs and symptoms, and severe toxic manifestations from the nitrogen mustard therapy were observed particularly in cases of acute rapid progression of the disease and in patients who were in the terminal stages of Hodgkin's disease after prolonged radiation therapy. In the latter, nitrogen mustard therapy appears to be contraindicated. With this exception, it is felt that this form of treatment can be applied with safety or a varying amount of benefit to many persons suffering from this disease.

The great advantages of nitrogen mustard therapy lie in their brief course, application far from centers of radiation therapy, and relatively low toxicity. The greatest benefit is derived in the treatment of multiple widespread manifestations of Hodgkin's to which radiation cannot practicably be applied. 4 references.

Some Observations on the Effect of Folic Acid Antagonists on Acute Leukemia and Other Forms of Incurable Cancer. *Sidney Farber, Children's Medical Center, and Harvard Medical School, Boston, Mass.* Blood 4: 160-67, Feb. 1949.

Temporary remissions in acute leukemia, as pronounced as those produced by aminopterin, have been effected by two compounds closely related chemically to aminopterin: these are amethopterin and amino-an-fol. All, however, are toxic compounds. The effective dose in children with acute leukemia is 3-5 mg. daily for amethopterin, and 25-50 mg. for amino-an-fol. The daily dose for aminopterin is 0.5-1.0 mg. The best guides to treatment are the daily white cell count and physical examination. Therapy should be discontinued if the white count drops too rapidly and if there is diarrhea, stomatitis, a sore tongue, or ulceration of the oral mucous membranes. During remission the doses are decreased slightly. Aminopterin is effective orally as well as intramuscularly. The most effective treatment in toxic reactions is suspension of the drug for four to seven days.

If toxic levels of folic acid antagonist are used long enough, the bone marrow may be sufficiently depressed to accentuate the hemorrhagic tendency in leukemia or to act as the sole cause of hemorrhage. The hemorrhage in leukemia may be caused by a number of factors apart from the effect of leukemic infiltrates on the bone marrow and viscera and the thrombocytopenia. Acute leukemia may be a form of cancer complicated by specific deficiency states.

In 60 children with acute leukemia treated for three weeks or more with folic acid antagonists, over 50% showed improvement. The remissions are dependent neither upon infection nor blood transfusions. The effect of the drugs is not limited to acute leukemia. There is still no evidence which would justify the word "cure" of acute leukemia. 11 references. 1 figure.

The Use of Folic Acid Antagonists in the Treatment of Acute and Subacute Leukemia: a Preliminary Statement. *William Dameshek, Pratt Diagnostic Hospital, and Tufts Medical School, Boston, Mass.* Blood 4: 168-71, Feb. 1949.

Thirty-five cases of acute and subacute leukemia in 4 children and 31 adults have been or are being treated with folic acid antagonists, including aminopterin, a-methopterin, amino-an-fol, and a-ninopterin. These, in sterile normal saline, were injected intramuscularly daily until a toxic or marked hematological reaction occurred; when the reaction subsided, a maintenance dose was given. The aminopterin dose was 1-4 mg. daily, a-methopterin, 2-5 mg., amino-an-fol, 25-75 mg., and a-ninopterin, 5-15 mg. Maintenance therapy was oral or intramuscular, and daily or every other day.

One case was treated less than four weeks, leaving 34 cases for analysis. Of these, 8 died one to five days after treatment. Excluding these, 26 cases are left: of these, 9 have had continued or intermittent remissions for at least two months and up to eight and one-half months. Best results were obtained in lymphoblastic cases, with respect to the proliferating cell type involved. None of the monocytic cases responded. Oral aminopterin, 1 mg. daily or every other day, was just as effective as parenteral medication. Toxic reactions occurred with aminopterin, depending in great part on the dose used and were in the nature of ulcerative mucous membrane and tongue lesions, nausea, burning sensation in the upper abdomen, and diarrhea. Other folic acid antagonists were less toxic but also less effective. It is believed that to obtain a remission it was necessary to produce toxic manifestations. In at least 1 case given a-ninopterin, therapeutic effects comparable with those of aminopterin were obtained with minimal toxic reactions.

Proliferation is not cured with treatment. Despite maintenance therapy, the leukemia and increasing toxicity to the drug make further progress impossible, and death follows. The results indicate that well-defined remissions in both leukemia and leucopenic forms can be secured in about a third of the cases in adults and children. Fulminating cases are only slightly affected, and best results are found with relatively subacute cases.

(The observations thus far reported indicate that the folic acid-antagonists now available are of little real value in the treatment of acute leukemia. The chief importance of this work is in encouraging a continued search for more effective preparations.—ED.*)*

Lymphoblastic Leukaemia Treated with Urethane. *D. Pullen, Royal Alexandra Hospital, Brighton, England.* Brit. M. J. 4594: 137-38, Jan. 22, 1949.

A case is described of acute lymphoblastic leukemia which responded initially to urethane therapy. One pint of blood was given to prevent death from anemia and 15 gr. of urethane was given orally three times daily. After a total of 51 gr., urethane was discontinued and another pint of blood was given to combat leukopenia. Apparent recovery suggested glandular fever—not lymphoblastic leukemia as originally diagnosed—but the Paul-Bunnel test was negative. The child was discharged clinically well but she deteriorated rapidly and died a month later.

Transfusion undoubtedly saved life initially, but clinical and hematologic improvement was far greater than could have been due to transfusion alone. Patients usually die despite adequate transfusion. Since no blood counts were done after discharge, it is uncertain whether the fatal outcome was due to the disease or to the toxic effect of urethane on myeloid cells. The large volume of blood given probably contributed to the remission, but the duration of this remission can reasonably be related to the use of urethane. 2 references. 1 table.—*Author's abstract.*

RECORD OF BLOOD COUNTS

Date	Haemoglobin, %	Total W.B.C.	Polymorphs, %	Metamyelocytes, %	Lymphoblasts, %	Lymphocytes & 'smudge' cells, %	Monocytes, %
21.7.47	42	27,700	2	—	98		—
23.7.47	28	5,500	4	0.5	12	83.5	—
1.8.47	58	11,900	37	—	2.5	58.5	2
13.8.47	66	5,700	60	0.5	2	32	5.5
22.8.47	60	4,000	61	—	—	35	4
1.9.47	110	5,400	42	—	—	57	1
9.9.47	102	5,200	67.5	—	—	30	2.5
23.9.47	100	18,150	76.5	2.5	—	18	3

Bone Sclerosis in Leukemia and in Non-Leukemic Myelosis. *Frank Windholz and Sidney E. Foster, Stanford University School of Medicine, San Francisco, Calif.* Am. J. Roentgenol. 61: 61-76, Jan. 1949.

Ten cases are discussed in which sclerosis of the skeleton, or of its parts, is associated with leukemia or non-leukemic myelosis. There were 3 cases of monocytic, 5 of lymphatic leukemia, and 2 non-leukemic chronic myelosis.

No basic differences were found between the symptoms and laboratory findings in cases of leukemia with bone sclerosis and those without signs of bone formation. The spleen and liver were always enlarged. The roentgenologic appearance of the bones varied according to location and structure of the densities. It was monostotic in 2 cases, polyostotic in 5, and panostotic in 3. Sclerosis in the long bones was characterized by thickening of the cortex and, occasionally, by dissociation of its texture. Panostotic sclerosis was more evident in non-leukemic myelosis than in lymphatic leukemia. The densities were frequently associated with periosteal proliferations. The marrow cavity was occasionally filled by new bone tissue. There were no basic differences in the histological appearance of the marrow in different forms of sclerosis.

The processes leading to sclerosis are: (1) leukemic infiltration of bone marrow; (2) disappearance of leukemic cells; (3) fibrosis replacing leukemic infiltrates; and (4) bone tissue forming in fibrous regions.

New bone lamellae form in fibrous marrow by metaplasia of fibrous interstices into woven bone structures. In monocytic leukemia fibrils form also as an exoplasmatic activity of leukemic cells; in other leukemias they form from adventitial and reticular structures. Periosteal bone shells follow the pattern of callus formation, preceded by minute destructions of the cortex. The reason for the formation of collagenous fibers, the precursors of osteogenesis, is obscure. The authors point out that an unknown toxin may give the first impulse to changes which produce sclerosis.

The roentgenologic signs of the sclerotic bone changes discussed should arouse the suspicion of leukemic changes. Monostotic and polyostotic sclerosis occurs most often in monocytic leukemia and in aleukemic lymphadenosis. Panostotic sclerosis characterizes non-leukemic myelosis; when associated with massive splenic enlargement, it definitely diagnoses non-leukemic, chronic myelosis. In panostotic sclerosis, splenectomy and roentgenotherapy are inadvisable and may produce death. Roentgenological signs of monostotic or polyostotic sclerosis in leukemia indicate that the bone marrow tends to become fibrous and aplastic; they do not indicate atypical leukemic course.

Areas of bone absorption in the cortex, which precede periosteal bone formation in long bones, may often become visible on x-rays. 42 references. 1 table. 13 figures.

Chronic Myeloid Leukaemia. Report of a Case Surviving Ten Years. *Alan J. Hird, University of Glasgow, Glasgow, Scotland.* Glasgow M. J. 30: 57-59, Feb. 1949.

A survey of the more important literature on chronic myeloid leukemia shows that it is rare for cases to survive more than 10 years. There follows a report of the clinical and hematologic features of the disease seen in a man of 42 who was followed for a period of almost 10 years. Deep x-ray therapy, principally to spleen, was given at intervals and is felt to have greatly prolonged both his useful and his total life. The effect on spleen and leukocyte count is shown graphically for the entire period. 6 references. 1 figure (graph).—*Author's abstract.*

Hemophilia: a Clinical Study of Forty Patients. *Charles S. Davidson, Robert D. Epstein, George F. Miller and F. H. L. Taylor, Thorndike Memorial Laboratory, and Harvard Medical School, Boston, Mass.* Blood 4: 97-119, Feb. 1949.

Observations were made on 40 patients with hemophilia, all males over 12 years of age. Twenty-eight had a definite family history of hemophilia. There were only 3 patients in whose family no hemophilia had appeared during three previous generations. There were 5 deaths, 3 of these from conditions unrelated to hemophilia. There were no deaths from acute blood loss.

Bleeding into joints is the most frequent event in adult hemophiliacs; 36 of the patients had chronic hemophilic joint disease, and almost all had acute hemarthroses. The knees and elbows were most often involved. In hemarthrosis, recovery from the acute phase usually begins after four to six days. Purpura is not characteristic of hemophilia. Ecchymosis and hematomata usually follow known trauma rather than appear spontaneously as they do in purpura hemorrhagica. Bleeding into or around bones is occasionally extensive and may interfere with the blood supply. This is observed chiefly in the hands or feet. Recurrent attacks of hematuria are very common and are generally spontaneous. Generally, the pain is typical of renal colic. No treatment affects the duration of hematuria. Hematoma formation beneath the mucosa of the pharynx and larynx is a rare emergency producing airway obstruction. Pulmonary and pleural bleeding are uncommon; massive hemothorax and hemoptysis are rare.

The usual acute abdominal conditions are a problem because of the high operative mortality. Certain forms of intra-abdominal and retroperitoneal hemorrhage so resemble acute surgical emergencies that the greatest diagnostic and surgical care must be taken to avoid fatalities. Peripheral nerve lesions are very common. Spontaneous intracranial hemorrhage is rare.

In treatment, the best agent is human whole blood or plasma less than 24 hours old, unless the plasma has been separated soon after phlebotomy and frozen. Human fibrinogen has antihemophilic activity, and Fraction I is

now in use. Moderate activity should be encouraged. Morphine should be avoided or else given for a minimal period. Aspirin with codeine is often effective. Thrombin is effective for local treatment of external bleeding. If surgery is necessary, there should be free use of blood transfusions and local application of thrombin.

In acute hemarthrosis, bed rest is necessary if the lower extremity is involved. Analgesia is usually indicated. During convalescence, radiant heat and whirlpool baths hasten recovery. The treatment of chronic hemophilic arthritis is largely orthopedic. Bed rest with immobilization of the part is necessary where there is a large hematoma of the soft tissues. Dental prophylaxis is important. Before extracting teeth antihemophilic globulin is given. Vocational training must be planned early in life. 110 references. 1 figure.

Hemophilia-like Disease in Women. Report of Two Cases. *James S. Hewlett and Russell L. Haden, Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, Ohio.* J. Lab. & Clin. Med. 34: 151-57, Feb. 1949.

The possible occurrence of hemophilia in women has never been conclusively determined, but several cases clinically resembling it have recently been reported. Two such cases are here reported. The first was a 40 year old woman who had a sudden hemorrhage into the base of her tongue. She gave a history of large subcutaneous hemorrhages with some swelling and pain in the right arm for 5 months previously, occurring several days after a bee sting on her right hand. The left arm had been similarly involved a week later. Irregular hemorrhagic episodes in different parts of the body followed. There was no family history of abnormal bleeding. Physical examination was negative except for many large subcutaneous hemorrhages over the entire body. Sternal puncture was negative except for an erythroblastic marrow. Laboratory findings are tabulated.

Six injections of plasma over a 3 month period caused an apparent improvement. A normal child was delivered 14 months later without abnormal bleeding. Continuous oozing followed a tooth extraction 3 months later and her entire jaw was black for a few days. No further evidence of bleeding or bruises occurred. Coagulation time had been reduced from 1 hour and 56 minutes to 15 minutes.

The second case was a 33 year old woman who had some swelling and tenderness of a finger joint without apparent cause. Later, there was some bleeding in the joint area followed by similar tenderness and hemorrhage of the right wrist and part of the arm. Large hemorrhagic areas then developed over the entire left leg and foot. A continued drop by drop bleeding occurred from the right nostril and she had hematuria for one week. Family and personal history were negative. Physical examination was negative except for ecchymotic areas on the right elbow, right and left thighs and left ankle. She received 250 ml. of lyophilized plasma intravenously and the coagula-

tion time was reduced from 2 hours and 15 minutes to 1 hour and 30 minutes. This procedure was repeated a few days later, and 6 months afterwards the coagulation time was 1 hour and 45 minutes. A telephone check two years later found her still having eccymoses and minor joint symptoms.

These 2 cases were clinically similar to true hemophilia, the outstanding characteristic being prolonged blood coagulation time. Coagulation time of recalcified plasma, believed by Quick pathognomonic for hemophilia, was positive in both patients. Coagulation in these cases was also greatly accelerated by the addition of normal citrated plasma to the blood of 1 patient. Tiselius protein fractionation showed definitely abnormal alpha-globulins in 1 patient and suggestive indications of abnormality in the second. It is suggested that some acquired change in the plasma protein pattern similar to that of hemophilia might be the basis for the coagulation defect in these patients. 27 references. 4 tables.

Some Experiments on the Treatment of Hemophilia with Mercury. *F. R. Bárány, St. Eric's Hospital, Stockholm, Sweden.* Acta med. Scandinav. 132: Fasc. II, 161-69, Dec. 8, 1948.

A patient with cardiac failure and massive edema was treated with frequent, repeated injections of a mercurial diuretic (mersalyl). In the course of this treatment, and apparently related to the injections, the patient developed multiple thromboses. This led to an evaluation of various mercurial preparations in their ability to influence the clotting time in persons suffering from hemophilia.

Six patients suffering from this blood disorder were available for experimental purposes. Mercurials were administered either by intravenous injection, intramuscular administration or inunction. Four of seven experiments with the intravenous injection of mersalyl yielded a significant reduction of clotting time, with a maximal reduction at about 24 hours after injection. Intramuscular administration of a mercurial suspended in oil (Ol. Hydrargyri) likewise yielded a marked reduction of clotting time which lasted for several days.

Two hemophiliacs received the salve, Ung. Hydrargyri, in amounts of 4 Gm. daily, rubbed into the skin for one week. There was a significant diminution of clotting time maintained during treatment. In two others no significant effect was observed. The amounts of mercurials administered had no adverse effect on kidney function nor on prothrombin time, thrombocyte count or fragility of platelets. The mechanism of this clotting action is not understood, but mercurials may be considered in the emergency therapy of hemophiliacs who are bleeding. 4 references. 3 tables. 4 figures (graphs).

Survival of Transfused Erythrocytes from a Donor with Nocturnal Haemoglobinuria. *J. V. Dacie and P. L. Mollison, Postgraduate Medical School of London, London, England.* Lancet 1: 390-92, March 5, 1949.

Four hundred and twenty ml. of blood (group O Rh+) were withdrawn from a donor suffering from nocturnal hemoglobinuria into 120 ml. acid-

sodium citrate-glucose diluent, and after a delay of 1 hour transfused into a patient (group B Rh+) suffering from rheumatoid arthritis and mild anemia. The survival of the transfused erythrocytes was studied by Dacie and Mollison's modification of Ashby's differential agglutination method.

5 months later when the donor's condition seemed to be similar he was bled again; 170 ml. of his blood was taken into 50 ml. of the same diluent. The blood was stored at 4° C. overnight and 35 ml. of a concentrated suspension was transfused to an anemic, but otherwise normal premature infant (group of A Rh+) weighing 5 lbs. As a control, 25 ml. of a concentrated suspension of A Rh— corpuscles were also transfused. The disappearance of the two populations of transfused corpuscles was studied separately.

The survival of the patient's blood was markedly impaired in the adult recipient; about 50% of the cells had disappeared within 5 days and on the tenth day only 30% were left. Thereafter, elimination was slow, 20% surviving for a further 20 days. In the infant, destruction of the patient's corpuscles was definitely slower than in the adult (although faster than that of the normal control cells). Almost 50% of the patient's corpuscles had disappeared by the twelfth day, but elimination was not complete until 80 days after transfusion.

The slower elimination in the premature infant was paralleled by the relatively slow hemolytic action of this serum on the patient's corpuscles in vitro. The hemolytic activity of the infant's serum in vitro was, in fact, less than that of 16 other sera from adults and infants. The demonstration that some of the patient's corpuscles had a relatively long life in vivo in both the adult and in the infant fits in with the observation that a proportion of the patient's corpuscles was resistant to hemolysis in vitro even by the most active serum encountered. 10 references. 3 figures (graphs).—*Author's abstract.*

Response of Lingual Manifestations of Pernicious Anemia to Pteroylglutamic Acid and Vitamin B_{12}. *James F. Schieve and R. W. Rundles, Durham, N. C.* J. Lab. & Clin. Med. 34: 439-47, April 1949.

While the therapeutic effectiveness of synthetic pteroylglutamic acid is satisfactory in the majority of patients with pernicious anemia, the macrocytic anemia is often not completely corrected and neurologic relapses may occur on maintenance doses. Little attention has been paid to the third major clinical manifestation of the disease, that of atrophy and inflammation of the lingual mucosa.

Seven patients with pernicious anemia in relapse having lingual mucosal atrophy were given 30-100 mg. of pteroylglutamic acid daily by mouth. In 2 patients the filiform papillae regenerated to normal height in 7-10 days, a response equal to that regularly obtained by fully potent liver therapy. In 5 patients the lingual response from the beginning of therapy was poor. Their tongues tended to remain red and the papillae stubby. During

the third month of pteroylglutamic acid therapy two of these had definite lingual relapses, developing sore, red and completely smooth tongues. They were given intramuscular injections of 0.010 and 0.025 mg. of vitamin B_{12}. Regeneration of filiform papillae and restoration of normal lingual color followed in 6-7 days.

Five patients with untreated pernicious anemia in relapse who also had lingual manifestations of the disease were given 0.001 mg. daily or a single dose of 0.010 mg. of vitamin B_{12}. Regeneration of papillae and restoration of a normal lingual color followed in 6-10 days.

Pteroylglutamic acid may fail to induce and maintain remissions of lingual manifestations of pernicious anemia as well as the anemic and neurologic. Vitamin B_{12} produced rapid regeneration of the lingual mucosa in patients with pernicious anemia who relapsed under pteroylglutamic therapy and in those who had no previous treatment. 31 references. 3 figures.—*Author's abstract.*

A Simple Quantitative Calcium-Formolgel Reaction, and Its Connection with the Euglobulin and Gammaglobulin Content of Serum. *B. A. Verhagen, University Clinic for Skin and Venereal Diseases, Amsterdam, The Netherlands.* Acta med. Scandinav. 132: fasc. III, 264-82, Dec. 31, 1948.

For many years the formol-gel reaction has been used as a simple qualitative test to indicate very marked increase in globulin. A new reaction is described which permits quantitative estimation of globulins.

The reaction is performed by adding to a series of tubes dilutions of the test serum in normal saline in a total volume of 1 ml. To this is added 0.1 ml. of a mixture of equal parts of 40% neutral formalin and 12% calcium chloride. The tubes are then stoppered with rubber corks and well shaken. After remaining undisturbed for 24 hours at room temperature the tubes are read by inverting them individually and noting the formation of a solid gel. The last tube showing complete solidification is taken as the end point of the dilution series.

A clear cut relationship could be demonstrated between the results of the calcium-formol-gel test and chemical estimation of both the total and the gamma globulin contents. In a series of 16 sera, electrophoretic analysis was carried out, and the results compared with those of the new reaction. Again it was found that the calcium-formol-gel reaction, performed quantitatively, permitted an approximate estimation of the gamma globulin content of a given serum.

It is felt that this new method can be of very marked assistance, particularly in the laboratory where electrophoretic, or other difficult determinations of proteins are not feasible, and may facilitate the diagnosis of diseases in which hyperglobulinemia is a distinctive feature. 12 references. 4 tables. 2 figures (graphs).

The Treatment of Carbuncles by the Local Injection of Penicillin. *Thomas H. Bate, Pheonix, Ariz.* Ann. Surg. 129: 494-98, April 1949.

By injection of penicillin and novocaine in the ratio of 100,000 units per cc., freshly mixed, into the periphery of the carbuncle in such a manner as to circumscribe the entire area, immediate relief of pain, rapid healing and negligible scarring has been obtained. The area of injection is the so-called cyanotic area. The penicillin and novocaine should be mixed immediately before using. There is no reaction between novocaine and penicillin A very fine hypo needle with a lock-type syringe is the best instrument for delivering the drug. The skin is carefully infiltrated, which requires considerable pressure, and the needle is then carried into the deeper tissues. Usually one to three treatments suffice in obtaining a cure. Hospitalization is not necessary and morbidity is greatly reduced.

9. Allergic Disorders and Diseases

Bacterial Allergy in Relation to Asthma. *Thomas P. O'Connor, Northwestern University Medical School, Chicago, Ill.* Arch. Otolaryng. 48: 145-49, Aug. 1948.

The author reports a study of 100 patients with allergic respiratory symptoms including 36 adults and 16 children with asthma and 48 children with allergic bronchitis or allergic rhinitis or both. In these cases there was clinical and bacteriologic evidence of active or latent nasopharyngitis. A combined treatment was used, first, to clear up the infection in the pharynx by local therapy; and secondly, the use of a bacterial filtrate, as nose drops, to stimulate the body's protective mechanism. For local treatment of the pharyngeal infection, a swab moistened with benzalkonium chloride ("zephiran chloride") in aqueous solution is used to remove the mucous film from the nasopharynx; then a 3 to 10% solution of silver nitrate is applied; and finally a solution containing 50% acriflavine, 25% methyl violet 2 B and 25% crystal violet in 1% concentration is applied with a swab. If results are not satisfactory after three or four treatments, a weak solution of iodine is substituted for the silver nitrate, and bacterial filtrate in a base of vanishing cream is applied in addition to the acriflavine mixture. After the nasopharyngitis is cleared up, the patient is given a bacterial filtrate with the instruction to use four drops in one nostril twice a week. This use of the bacterial filtrate can usually be begun in children after the second treatment for the pharyngitis, but in adults not until after the sixth treatment.

The bacterial filtrates employed are stock filtrates, prepared from cultures of organisms obtained from the throats of patients with acute and chronic pharyngeal infections. Such filtrates are prepared from each of the following organisms: Streptococcus viridans, hemolytic and non-hemolytic streptococci, pneumococcus, staphylococcus, Neisseria catarrhalis and Hemophilus influenzae. For use as nose drops, the stock filtrate is diluted 1: 36,000

with sterile isotonic sodium chloride solution. The filtrate used in each case depends upon cultures obtained from the patient's nasopharynx. If an asthmatic attack is precipitated by the use of the filtrate, the dilution is still further increased.

Of the 100 patients in this series, 22 had been under the care of allergists and had been given the usual desensitizing treatment without improvement. Of the 52 patients with asthma, 19, or 36.6%, have been entirely relieved of symptoms for periods of 1 to 6 years; 29, or 55.7%, have been free from symptoms for the most part, but have an occasional recurrence after an acute infection of the respiratory tract. The results, therefore, may be considered good or fair in 92.3% of the cases of asthma. Of the 48 allergic children, only 32 have been followed up; of these, 14, or 47%, have been entirely relieved of allergic symptoms; and 12, or 37.5% have no symptoms except occasionally after a respiratory infection; so that results are considered good or fair in 84.5% of these cases. Three illustrative cases are reported.

New Trends in the Treatment of Bronchial Asthma. *George L. Waldbott, Detroit, Mich.* M. Clin. North America 33: 411-25, March 1949.

There is evidence that an asthmatic attack is a defense reaction designed to ward off and render innocuous harmful antigens similar to an infectious process which localizes and neutralizes harmful bacteria. Where this defense is lacking, human anaphylactic shock (formerly called "thymic death") is likely to occur. This results from inhalation, ingestion and injection of antigens to which excessive sensitivity exists. Treatment of asthma should therefore be directed not only toward control of symptoms but also to interfering as little as possible with the natural mechanism of the defense reaction.

In asthma, four situations arise, each of which requires a different therapeutic approach:

1. For the emergency, large doses of epinephrine, intravenous aminophyllin and antihistaminics are the method of choice. The most common causes of emergencies are ingestion of salicylates, of such foods as fish, nuts, cottonseed; inhalation of animal hair, of dusts from organic and non-organic chemicals; therapeutic injections of biologicals.

2. In treating the chronic asthmatic state the following facts should be taken into account: Chronic asthma is usually initiated at, or shortly after, the pollen seasons. Food is a minor factor, except when gastro-intestinal symptoms are present and in early childhood. Cessation of symptoms follow-administration of certain measures does not indicate that this measure is responsible for the so-called cure. Prolonged use of any drug is likely to aggravate asthma; its discontinuance may lead to the patient's improvement. The principal measures to control chronic asthma are eliminative procedures, short interval hyposensitization, control of infection (antibiotics) and such medications as epinephrine, aminophyllin, antihistaminics and iodides,

which relieve bronchospasm, increase expectoration, and thus eliminate antigenic material from the bronchial tree. Routine and persistent administration of antihistaminics is as harmful as that of other drugs. Oxygen, carbon dioxide and helium may relieve dyspnea but occasionally increase the patient's symptoms. Counteracting dehydration by large amounts of fluids, glucose and amino acids as well as by giving blood plasma are advocated. Bronchoscopic lavage is probably the most effective means to arrest chronic asthma.

3. For the state of rehabilitation, it is necessary to discontinue or reverse many measures which had been previously useful in order to prevent a psychosomatic aggravation of the disease. High caloric diets are indicated in order to improve the patient's nutritional state. Systematic exposure to inhalant antigens to which the patient had been sensitive before tends to adjust his tolerance to normal surroundings. The threshold of tolerance to effort is improved by light exercise, gradually increasing in scope. In order to counteract the effect of sudden temperature changes he should gradually build up his tolerance to cold by sponging legs, arms and later the whole body surface with cold water and applications of ice. A change of climate should not be advocated unless a thorough analysis of the prospective climate is made. This "last resort" in the patient's management will lead to despondency and despair if not successful.

4. Complications of asthma require individualized treatment. The most common complication is pneumonitis which may be followed by fibrosis of the lungs or by segmental bronchiectasis. Massive generalized bronchiectasis as a complication of asthma is much less common than indicated by the literature. Subcutaneous emphysema, mediastinal emphysema, spontaneous pneumothorax, cystic degeneration of the lungs, spontaneous rib fractures occur as a result of severe coughing spells. Convulsions in children, or sudden syncope lasting for a few seconds in adults are due to anoxemia. 10 references. 2 tables. 3 figures (graphs).—*Author's abstract.*

Allergic Dermatitis due to Handling of Streptomycin by Hospital Personnel. *(Les dermites allergiques de la streptomycine parmi le personnel infirmier). A. Touraine and R. Pichon, Paris, France.* Presse méd. 56: 855-856, Dec. 11, 1948.

Among staff members handling streptomycin, especially nurses preparing material for injection, there has been an increasing incidence of dermatitis on skin frequently exposed to the antibiotic. The frequency of this disorder varies in different reports, from 5% to as high as 57% of exposed nurses.

Apparently, allergic tendencies in the past did not contribute to the development of this dermatitis: Only 4 of the individuals who developed streptomycin reactions had a previous history of skin disorders; therefore

prolonged handling of streptomycin appeared to be the factor for the development of dermatitis. In only 16% of the cases did dermatitis appear within less than 1 month after the individual began handling streptomycin; in 52% it appeared 2 to 6 months after, and in 20% it took a full year to develop.

In 70 observed cases there were occasional prodromal systemic manifestations, particularly vertigo, nausea, and headaches. Many individuals manifested a blepharoconjunctivitis as the earliest manifestation of sensitivity. The conjunctivitis is often mild or minimal, but the lids become swollen and pruritus may be intense. The dermatitis takes the form of an eczema, appearing practically always first on the hands or face. Pruritis is often intense, leading to secondary changes as a result of scratching. Under conservative therapy and immediate removal from contact with streptomycin the lesions commonly subside, but occasionally there is marked chronicity with lichenification or scarring if they become inpetiginized.

After lesions have cleared sensitivity to streptomycin persists, and re-exposure leads to relapses of considerable severity.

Untoward Reactions Encountered in the Course of Penicillin Therapy. *(Les accidents au cours de la pénicillinothérapie).* *G. Ménégaux, M. Courtois-Suffit and C. Crépy, Paris, France.* Progrès méd. 76: 244-247, May 24, 1948.

Even the indiscriminate, widespread use of penicillin has given rise to remarkably few untoward side effects. In view of the increasingly larger number of individuals given this drug, an increasing number of reactions must be expected. The reactions commonly observed are of the following types.

Most frequently a febrile reaction is encountered in the course of administration of the drug. This practically never occurs on the first administration but usually is seen 10 to 14 days after beginning of therapy if injections are given daily, or 1 to 3 days after the start of a second course of penicillin. The febrile reaction commonly poses the problem of differentiating whether the origin of the fever is the underlying disease for which the antibiotic is being given, or the drug. The decision can be made quickly by discontinuing the therapy for 18 to 36 hours in which case the fever will promptly disappear, or by observing the continuing improvement of the patient in spite of the febrile reaction. Bacteriologic studies are often helpful. Examples of this type of reaction are given.

The second type of penicillin reaction frequently observed resembles serum sickness. It consists of a generalized urticarial rash, angioneurotic edema, arthralgia, and occasionally fever, starting 10 to 14 days after penicillin injection, independent of its continuity. This is often aggravated by renewing injections for the "disturbance". It is self-limited and responds favorably to medication with antihistaminics. With the newer crystalline penicillin preparations in aqueous solution it is rarer than with early impure preparations or those in beeswax-peanut oil.

The main third type of reaction consists of other cutaneous eruptions, non-urticarial, occasionally scarlatiniform, but most frequently evidenced by an aggravation of already present skin lesions.

The pathogenesis of the various reactions is not altogether clear, but may be multiple. Some of the reactions are almost certainly a function of impurities in the preparations and are largely eliminated in the newer forms of crystalline penicillins. However, in the reaction resembling serum-sickness penicillin itself may be well responsible, perhaps causing an antibody response to a drug serum protein complex and resulting in an antigen-antibody reaction of the allergic type. True idiosyncrasy to penicillin has probably also been observed on rare occasions. It appears likely, however, that the majority of reactions to purified penicillins are true allergic reactions and must be guarded against by limiting administration of the drug to cases in which it is properly indicated and by other measures suitable to prevent sensitization whenever possible.

10. Deficiency Diseases and Metabolic Disorders

Heredity in Diabetes. Report of Five Generations of a Diabetic Family. *Norman Burnstein and McLeod Patterson, New Orleans, La.* South. M. J. 42: 119-20, Feb. 1949.

The factor of heredity in the etiology of diabetes mellitus has been accepted without question, but in spite of more than twenty years of statistical study it has been impossible to establish it as the primary factor. The "unitarian" school has accepted this principle but has left many others unconvinced. Granting its importance in the etiology of diabetes, whether as the primary or merely as a contributing cause, the hereditary factor has not yet been shown to operate in any constant genetic pattern. Varying opinion would have it act as a recessive trait, as a sex-linked tendency, or as an alternating dominant.

There is presented the lineage of a family from the time of the marriage of two diabetics. The succeeding four generations have included 161 persons, of whom 55 have been diabetic. The phenomenon of anticipation is well demonstrated in that the disease develops at an earlier age in successive generations. The average age at onset has progressively decreased from 59 in the parents, to 48, 26 and 10 in the succeeding generations. The fourth generation is as yet free of diabetes. Contrary to expectation only five of the ten members of the first filial generation became diabetic, although four of the others lived to rather advanced ages. Of the female members, 44% have been diabetic, in contrast to a 22% incidence in the males. To our knowledge no diabetes has been introduced into the family by subsequent marriages, but this possibility is of course not excluded. Consequently the evidence that diabetes is transmitted as a type of mendelian dominant in this family is only suggestive. 6 references.—*Author's abstract.*

Principles of Nutrition Therapy. *Robert S. Goodhart, The National Vitamin Foundation, Inc., New York, N. Y.* Bull. New York Acad. Med. 25: 185-93, March 1949.

The four cardinal principles of nutritional therapy are (1) early treatment; (2) the use of therapeutic amounts of prescribed nutrients; (3) the provision of all of the nutrients necessary for life and health in effective quantities and in forms utilizable by the patient; and (4) continuous and prolonged treatment. Nutritional disorders are most susceptible to correction before anatomical lesions develop. The importance of early treatment, therefore, cannot be over-emphasized.

The diagnosis of early nutritional deficiency states requires as careful appraisal of the patient's medical and dietary history as of his symptoms and signs. For sound judgment regarding the need for preventive measures, the medical and dietary histories are all important.

A sharp distinction must be made between the prevention of nutritional deficiencies and the cure of existing nutritional deficiency states. The most efficient therapeutic amounts of the vitamins generally range from five to ten times maintenance amounts. Protein needs for depleted tissues are considerably greater than those for maintenance. 125 Gm. daily might well be regarded as the minimal therapeutic dose in the adult.

For the efficient utilization of dietary protein for body building, the protein consumed at each meal period should be complete. In addition to adequate protein and calories, adequate amounts of the vitamins, particularly those of the B complex, are necessary for tissue synthesis. In contrast to their value for the replacement of blood losses or for the correction of anemia, whole blood and plasma as sources of parenteral protein food are both expensive and unphysiological. The injection into the blood stream of an appropriate mixture of amino acids is a physiologic method of alimentation. 9 references. 1 table.—*Author's abstract.*

The Problem of Posttraumatic Diabetes. Anatomical and Clinical Documents of the War. *(Le problème du diabète traumatique. Documents anatomocliniques de guerre.) R. Ramniceanu, Bucharest, Roumania.* Presse méd. 57: 87-88, Jan. 22, 1949.

In the opinion of many experts, trauma should be disregarded as one of the possible etiologic agents of diabetes mellitus. There are, however, many instances known in which trauma was closely associated with the manifest onset of this disease.

In theory there are three essential forms of trauma which could contribute to the development of diabetes: (1) trauma to the head, with resulting injury to the pituitary, hypothalamus, floor of the third ventricle, or other structures participating in the endocrine regulation of carbohydrate metabolism; (2) trauma to the epigastrium or umbilical region, involving in some fashion the pancreas or its blood supply; (3) shock due to the

explosion of bombs, mines, etc., resulting in concussion, compression and other injuries, without clear-cut localization. Emotional shock must likewise be included here.

The relationship of the anterior pituitary to other endocrine glands important in carbohydrate metabolism is sufficiently understood to make trauma to the head an occasional plausible explanation for the onset of diabetes mellitus. Such instances are quite rare in clinical practice, but much experimental evidence supports this possibility.

The nature of the lesion inflicted upon the pancreas by direct injury is less certain. It seems likely, however, that hemorrhage, necrosis, interference with blood supply, or perhaps late fibrosis could all lead to serious degeneration of the islets of Langerhans with consequent deficiency in insulin production.

Two cases are reported illustrating the sudden onset of diabetes after an individual sustained a war wound.

The Blood Sugar in Diabetic Coma. *(La glycémie dans le coma diabétique). R. Boulin, Paris, France.* Presse méd. 56: 753-754, Oct. 30, 1948.

It is commonly assumed that in diabetic coma a marked hyperglycemia is the rule. It has been pointed out in some series that the average blood sugar level is 440-540 mg.% and the highest levels are between 1,600 and 1,850 mg.%. To explain these enormous levels, it is usually postulated that very active gluconeogenesis (i.e., formation of glucose from fats and proteins) is taking place, since pre-acidotic individuals usually are anorexic and their intake is small.

In other series of cases, however, the findings are different. Among 81 patients in diabetic coma reported, 5% had blood sugar levels of less than 200 mg.% and a total of 23% had levels below 300 mg.%. It appears possible that in these individuals the mechanism of gluconeogenesis may have been impaired, and their precoma alimentation quite poor.

This finding reflects on the old discussion as to whether or not individuals in diabetic coma should occasionally be given intravenous glucose in order to cover the large doses of insulin they have to receive. Joslin, Root and their colleagues insist that glucose should never be injected because in diabetic coma sufficient glucose is available in the body and injected glucose is not utilized, and may contribute to oliguria and anuria.

These statements should not go unchallenged. For while unquestionably there is enough sugar available if the level is 400 mg. or more per 100 mil., it would hardly be adequate with blood levels of 200-300 mg.% when 200 to 300 units of insulin are administered during the first hour. The danger of renal damage appears remote, and consequently isotonic glucose solution in saline is employed routinely by many. With hypertonic solutions of glucose central nervous system symptoms have been observed, perhaps attributable to cerebral edema, and such materials have been abandoned.

It should, of course not be inferred that there is no relationship between the degree of hyperglycemia and the acidosis. There is a clear-cut linear inverse relationship between the blood sugar levels and the average alkali reserve.

An important characteristic of the blood sugar levels in diabetic coma is their extreme instability. During the first few hours one may give very large doses of insulin without fear of hypoglycemia, and without supplementary glucose. Then, however, the patient may abruptly, and without any warning signs or symptoms go into hypoglycemic shock. The explanation for this occurrence is not clear, but it emphasizes the necessity of observing the blood sugar levels carefully during insulin therapy and suggest the relatively free use of isotonic glucose solutions early in the treatment.

Simultaneous Diabetic Coma and Cavernous Sinus Thrombosis. Report of a Case. *Thomas H. Connell, Jr., (Lt., j.g., M.C., U.S.N.R.)*, U. S. Nav. M. Bull. 49: 55-8, Jan.-Feb. 1949.

This patient was a 23 year old white woman admitted to the hospital in coma. Her history showed a 30 lb. loss of weight in six months and progressive polydypsia, polyphagia and polyuria. She had taken sulfonamide pills for a painful, draining right ear. Examination showed a diabetic acidosis and active chronic otitis media of the right ear. The right eye showed only slight light reaction, a blurred disk and some retinal pallor, no corneal reflex, and an immobile globe. The left eye was normal. Neurological examination showed decreased deep reflexes, absent abdominal reflexes and paresis of the right third, fourth, sixth, and ophthalmic branch of the fifth cranial nerves. The spinal fluid pressure was markedly reduced but both smear and culture were negative. Culture from the right ear showed hemolytic staphylococcus aureus. Blood cultures were negative.

She was given 100 units of regular insulin immediately, followed by 50 units every hour. The blood sugar rose to 824 mg. per 100 cc., however, in eight hours. An additional 150 units of regular insulin was given plus 8,000 cc. of isotonic saline solution. This treatment controlled the diabetes, but the intracranial condition became worse with a temperature of 105° F. A diagnosis of cavernous sinus thrombosis with occlusion of both the ophthalmic artery and vein was made. The patient's dehydration was corrected, 50,000 units of penicillin given every 3 hours and sodium sulfadiazine 12 Gm. intravenously each 24 hours. Intravenous heparin was also administered. She responded temporarily, but died the fourth hospital day. Autopsy was refused.

This patient showed marked insulin resistance the first day, but the diabetes was then controlled. After the expected thrombosis of the ophthalmic vein and tributaries following development of the cavernous sinus thrombosis, however, sudden and complete occlusion of the right ophthalmic artery developed. This was followed by gangrene and advanced degeneration of all

the orbital contents, periorbital spin and nasopharynx. The exact cause of death could not be determined without autopsy but multiple septic emboli and septicemia were thought possibly responsible. 11 references.

The Cyclical Desquamation of the Epithelium in the Urinary Tract Corresponding to the Menstrual Cycle. *(La desquamation cyclique de l'épithélium des voies urinaires en rapport avec le cycle menstruel). L. L. Wasserman, Laboratory for Medical Physiology, University of Jassy, Jassy, Roumania.* Presse méd. 56: 755-756, Oct. 3, 1948.

On the basis of 30,000 examinations on clinic patients it has been determined 1) that there is no relationship between the intensity of the desquamation of the epithelium of the urinary tract and the presence of urinary tract infection from the pelvis down; 2) that this desquamation is of very low order in the male; and 3) that it is exceedingly variable in the female.

In order to investigate the possible relationship of hormonal influences and shedding of urinary tract epithelium a systemic study was undertaken. Morning specimens were secured from various groups of females, either by catheter or after thorough cleansing of the external genitalia, and the centrifuged specimens were examined microscopically in a semi-quantitative manner.

In a group of 11 girls aged 1 to 7 years the urines were examined every other day for 35 days. The number of epithelial cells was uniformly very low, the average being always below 20 per field.

The second group consisted of 28 girls between the ages of 9 and 15 years. Five of these girls had begun to menstruate irregularly. There was a marked difference between the sediments of the girls before menarche and after onset of menstruation. In the former the levels of epithelial cells were uniformly low, resembling the younger age group. In the latter, however, there was a clear-cut and unmistakable five to ten-fold rise in the number of epithelial cells 4 to 8 days prior to the onset of a menstrual period, with a following sharp drop to normal levels at the beginning of menstrual bleeding.

In the third group of 20 girls aged 16 to 23 years, all of them menstruating, fairly uniform curves were obtained. There was regularly a high peak of desquamation just preceding the menstrual period, and falling abruptly to normal as bleeding starts, or 24 hours earlier.

Among 10 women aged 57-76, all after the menopause, the level of epithelial desquamation was very low and quite comparable to that seen in very young children. Observations in the course of pregnancy indicated a rather uniformly high level of desquamation from the second to the ninth month.

On the basis of these observations it is concluded that the desquamation of urinary tract epithelium is definitely governed by hormones which influence the menstrual cycle. The level of desquamation is low until the rupture of the graafian follicle, then gradually rises to reach a peak just prior to onset of menstrual bleeding, and drops abruptly to normal levels. This is taken to indicate that desquamation is essentially a function of ovarian hormones. 6 references.

Menstrual Disorders in Pellagra. *F. Mainzer, the Jewish Hospital, Alexandria, Egypt.* Acta med. Scandinav. 132: fasc. IV, 384-91, Jan. 20, 1949.

Among 11 women of childbearing age, suffering from pellagra, menstruation was normal in only 1 patient. Amenorrhea was present in 3, menorrhagia or metrorrhagia in 4, and in the remaining 3 patients a reliable history could not be obtained.

Experimental and clinical observations have shown that of the organs concerned with the sexual cycle the function of the anterior pituitary, the adrenals and the liver are impaired by vitamin B deficiency. There is evidence strongly pointing to a pituitary origin of the amenorrhea in pellagra. Arguments are put forward supporting the view that the menorrhagia and metrorrhagia in pellagra are due to insufficient inactivation of estrogen resulting from impaired liver function. The roles of adrenal damage present in pellagra and of ovarian failure induced by a hypothetical direct influence of the deficiency state are discussed. Further investigations in pellagrins by means of biopsy of vaginal mucosa and endometrium and by estimation of the urinary output of gonadotropic hormone, estragen, 17 keto-steroids, creatinine and phosphorus are suggested. 46 references. 2 tables.—*Author's abstract.*

Fetal Organ Grafts in Endocrine Deficiency. *(Greffes foetales dans l'insuffisance endocrinienne). J. Villar, M.A. Blum and L. P. Doutre, Bordeaux, France.* Presse méd. 57: 342-343, April 16, 1949.

Therapy of deficiency states of organs of internal secretions relies largely on the administration of more or less purified products and extracts of glands of internal secretion. Occasionally, synthetic substances are used for substitution therapy. Ideally, however, it should be possible to replace the non-functioning, or absent gland with a living graft.

Many years of experimentation have indicated that only homologous grafts of such organs would have a chance of survival. If such homologous grafts could be made to take, they would be more preferable than any other type of substitution therapy. The best source of endocrine gland tissue was found to be not adult tissue removed at operation or immediately post-mortem, but rather, the glands of a prematurely delivered fetus, soon after death.

The largest experience relates to attempts at transplantation of fetal thyroid to children suffering from cretinism or myxedema. In other cases the pituitary gland was also grafted. The glandular tissue was cut into small pieces with scissors, and inserted into well vascularized subcutaneous tissue of the recipient, taking care of complete hemostasis to prevent necrosis of the graft.

Three recipients of such grafts are reported who received combined thyroid-pituitary grafts. In two children, aged 10 and 17 who previously were cretins, unable to read, write or attend school, the progress was significant, with marked intellectual and physical development. In the third case the initial progress was good, but the grafts apparently underwent necrosis and resorption in the course of bronchopneumonia two months later. It is felt that the method offers some promise.

11. Nervous and Muscular Disorders and Diseases

The Landry-Guillain-Barré Syndrome. A Clinicopathologic Report of Fifty Fatal Cases and a Critique of the Literature. *Webb Haymaker and James W. Kernohan, Army Institute of Pathology, Washington, D. C. and Mayo Clinic, Rochester, Minnesota.* Medicine. 28:59-141, Feb. 1949.

A clinical study of 50 fatal cases of a disorder variously referred to as Guillain-Barré syndrome, acute infective polyneuritis, Landry's paralysis, and otherwise, confirmed the impression gained from a review of the literature that all fall into a single category. Practically all the different forms of the disorder which have been recognized by others are represented in the present series. Taken as a whole, the disorder is characterized by a polyradiculoneuropathy which may begin in any peripheral neurons, spinal or cranial, circumscribed or widespread; it may affect predominantly the motor or the sensory neurons or both to the same degree; it may remain essentially a radicular disorder; or, according to some authors, it may extend into the central nervous system at any point, and either ascend or descend, the outcome usually being dependent on the degree of involvement of respiratory or cardiac nerves.

In the present series systemic or local infections ushered in the disorder in 40. A latent period between the occurrence of prodromal symptoms and neural attack was observed in 9 of the series. In only 3 instances was there a definite febrile course. In most of the cases the disorder involved the limbs before it became generalized in the domain of the cranial nerves, trunk and intercostals. The incidence and severity of sensory symptoms tended to increase in accordance with the duration of the disorder. Respiratory failure, which could usually be traced to intercostal paralysis, was the final event in the great majority of cases, and in 3 circulatory failure was regarded as the cause of death. Cranial nerves were affected in all cases except 3. Dysphagia developed in 43 and dysarthria and/or aphonia in 33.

Palsies of cranial nerves other than the ninth and tenth occurred in the following order of frequency: seventh in 25 cases; fifth in 14; third, fourth and/or sixth in 12; and the twelfth in 10.

Spinal fluid studies included total protein determination in 33, and the Pandy reaction in an additional 5, making a total of 38. Protein was increased in 27, or 79% of the 38 cases, the amount varying from 50.5 to 375 mg.%, and exceeding 150 mg.% in only 6. The over-all clinical picture and the duration of the disorder in cases with normal spinal fluid protein differed in no essential from those in which it was elevated. Total and differential leukocyte counts of the blood were available in 22 cases, excluding the 2 associated with infectious mononucleosis. In 12 of these there was a relative and an absolute increase in lymphocytes early in the course of the disorder, the total number varying from 3,900 to 8,281 and the percentage values from 25 to 80.

It is of great interest that malignant hypertension developed during the course of the illness in one-fifth of the cases, an observation which should lead to a reinvestigation of the role of the spinal roots and cranial nerves in the development of hypertension.

Study of the central nervous system revealed nothing of consequence in the spinal cord, brain stem, or cerebrum, aside from mild to moderate and occasionally severe changes in anterior horns of the spinal cord and motor nuclei of the brain stem, which were regarded as retrograde. The peripheral nervous system, on the other hand, was consistently affected, the lesions being concentrated in the spinal nerves, i.e., in the region where the anterior and posterior roots fuse, and extending for a short distance proximally and distally. The study afforded the opportunity of determining the approximate sequence of the changes: edema during the first 3 or 4 days, beginning swelling and irregularity of myelin sheaths and axis cylinders on the fifth, appearance of a few lymphocytes on the ninth, and phagocytes on the eleventh, and Schwann cell proliferation on the thirteenth. The changes in myelin, axis cylinders, and Schwann sheaths were progressive, so that by the forty-sixth day, the maximum duration in the present group, some of the spinal roots and peripheral nerves were devastated.

The most striking change elsewhere was in the lungs, where bronchopneumonia usually in any early stage, was encountered in 33 cases.

No conclusive evidence of the etiology of the disorder is presented, although the association of infectious mononucleosis has been proved in 2 cases and suggested in 6 of the present series. 225 references. 10 tables. 17 figures.

Investigations of the Pathologic Physiology of Amputation Stumps. Studies of the Spatial Modifications of Phantom Limbs. *(Recherches sur la physiologie pathologique des moignons d'amputation. Etudes sur les modification spatiales des membres fantômes.)* *A. Jung, Strasbourg, France.* Progrès méd. 76: 275-278, June 10, 1948.

A majority of amputees with phantom limbs can specify quite accurately the length of the phantom. When repeated examinations are carried out, they can indicate the length with great constancy under similar conditions. Usually, the length of the phantom limb is inversely proportional to the length of the stump. The shorter the amputation stump, the longer the phantom limb.

When a weight is suspended from the amputation stump held horizontally, near its end, the phantom limb appears to become shorter. A similar shortening almost always accompanies the injection of the skin and muscles of the amputation stump with local anesthetics.

Infiltration of the stellate ganglion (in the case of arm amputation) appears to lengthen the phantom limb. In the case of bilateral amputation, this procedure lengthens the homolateral and shortens the contralateral phantom.

A number of cases are presented of patients in whom this experiment was performed with rather constant results. A possible explanation of this phenomenon can be sought in the vascular effects of the procedures employed. Infiltration of the stellate ganglion results in homolateral vasodilatation and contralateral vasoconstriction. This might indicate that the effect of peripheral vasodilatation is opposite to that of the cerebral centers.

The infiltration of sympathetic ganglia, especially the stellate ganglion, may be useful in a number of sufferers from phantom limb. Such injections are followed by a feeling of relaxation and of subjective improvement. The phantom often becomes less painful, less stiff and appears to move.

The effects of infiltration have been more effective and consistent in amputation stumps of upper than of lower extremities. However, even in the latter, some useful applications of this technic were found. A number of amputees who employed a leg prosthesis but suffered from pain in the phantom limb, were given sympathetic chain infiltration which relieved the pain and gave them the sensation that each was walking on his own leg again.

An Unusual Case of Hemiplegia. *(Une curieuse histoire d'hemiplegie). P. Cossa, Nice, France.* Presse méd. 56: 787, Nov. 1948.

A 10 year old boy was brought to the hospital with a partial left hemiplegia. The child had been well in the past except for the usual diseases of childhood. Five days prior to entry the child had found an unexploded grenade half a mile outside his village; picked it up, and thrown it away just as it exploded. He was terribly frightened and ran back to the village where he collapsed and fell unconscious. There was a small wound in the right side of the neck which did not bleed significantly.

The wound, a few days later, was found to measure only 5 mm. in length, located between the two heads of the sternocleidomastoid muscle. There was spastic paralysis of the left arm, held in flexion, and partial paralysis of the left leg in extension.

It was originally assumed that the child suffered from some form of encephalitis or encephalomyelitis, presumably of infectious origin, possibly from a brain abscess or a vascular accident of unknown etiology. However all diagnostic procedures remained essentially negative except for x-rays of the skull. These showed a foreign body lodged in the region of the carotid canal and apparently within the carotid artery.

The explanation of this curious hemiplegia apparently is that the boy sustained a wound from a grenade fragment which entered the carotid artery. The wound apparently did not bleed because of the block of the fragment. That 8 minutes elapsed between injury and loss of consciousness due to vascular obstruction, can be attributed to the fragment being gradually carried in the carotid lumen toward the base of the skull. The boy ultimately regained use of the extremities, and the fragment continued to remain in its place.

Abscess of the Cerebellum *(Les abcès du cervelet). C. Gros., Paris, France.* Progres méd. 76: 200-203, April 24, 1948.

There have recently been such significant changes in the treatment and prognosis of the various forms of brain abscess as to warrant review of the material. While the first successful surgical results in the treatment of brain abscess were obtained in 1887, recent progress in chemotherapeutic approach has modified all aspects of the disease.

Etiology. They occur rarely following trauma, are occasionally metastatic following infection of the blood stream, but most commonly occur as a sequelae to suppuration in the middle ear, in the labyrinth, or the lateral cranial sinus, with thrombosis. The offending organism is commonly a pyogenic gram positive coccus.

Anatomically, there is a gradual trend toward walling off the infected area. In the initial stage there is often widespread encephalitis with a marked meningeal reaction around the affected lobe of the cerebellum. There is perivascular infiltration with inflammatory cells and thrombosis of small vessels, with a good deal of cerebellar edema. As the inflammatory lesion continues frank suppuration appears, with necrosis in the center of the forming abscess. The surrounding tissues show gliosis in the progressive tendency to wall off the abscess which finally gives the appearance of an encysted tumor in the cerebellar substance. Occasionally, this process of walling-off does not progress satisfactorily, but the inflammatory reaction remains generalized, with the formation of widespread basal meningitis, multiple abscesses, etc.

The typical clinical picture is seen in a child recently suffering from otitis, who develops fever and signs of meningitis with stiff neck, and a positive Kernig sign. Lumbar puncture reveals usually turbid fluid under increased pressure, with less than 500-1000 cells per cu. mm., and no bacteria whatsoever.

Under therapy with sulfonamides and penicillin the patient often shows great improvement, but some headache remains, and gradually the patient fails again and loses weight and strength. In addition, there frequently develops evidence of increasing intracranial pressure, with intractable headaches, papilledema, and paralysis of the sixth nerve. Localizing signs are not usually prominent. However, one can find evidence of increasing dysmetria, dyssynergia, adiadochokinesia, slow nystagmus, past pointing, and hypotonia.

At this stage the patient is in extreme danger from sudden rupture into the subarachnoid space, with resulting overwhelming meningitis, and from respiratory arrest due to high intracranial pressure. Lumbar puncture is very hazardous in such patients. It may lead to herniation of the medulla, and compression of vital centers and immediate death.

Differential diagnosis has to take into account mainly generalized meningitis, temporal lobe abscess, and cerebellar tumor. Lumbar puncture in the initial stage differentiates the first of these conditions. In temporal lobe abscess there is hemianopsia, epileptiform attacks, frequently aphasia, and hemiplegia. Tumor of the cerebellum can be differentiated only if there is response to chemotherapy or at operation.

In untreated cases the mortality has been estimated at more than 50%. The antibiotics, particularly penicillin, can sterilize the infection in the early stages when used systemically. When the abscess has formed, injection of antibiotics into the cavity may sterilize it also. However, such chemotherapy cannot cure the more advanced stages of the illness, unless the abscess is drained surgically, or resected — under chemotherapy — in toto.

A Syndrome Resembling Acrodynia in Young Females *(Le syndrome aerodynique des jeunes filles). M. Porot, Algiers, North Africa.* Presse méd. 56: 709-10, Oct. 9, 1948.

Three cases are reported of girls aged 14, 17, and 23, who uniformly after a minor febrile episode or psychic disturbance suddenly developed a severe anxiety state followed by fever and the appearance of erythema, paresthesias of the skin of the hands and desquamation.

All of them had been of a "nervous" type in the past, but aside from childhood diseases essentially well. The sudden onset of the anxiety state was often associated with hallucinatory experiences, formication of the skin, and rapidly followed by fever up to 40° C.

The cutaneous manifestations commonly appeared first on the palms of the hands where the erythema was dull red, often associated with some edema. There was, however, no local tenderness associated with the paresthetic sensations. Hyperesthesia of the skin of the rest of the body was occasionally very marked, making management difficult.

The combination of severe psychic disturbances associated with vasomotor disturbances, suggestion of peripheral neuritis, the typical erythema and the paresthesias all suggested acrodynia as the diagnosis of

choice. However, there was no hypertension, the course was rather short, and the age of the patients spoke against such a decision. The spinal fluid in all patients was entirely normal.

Two of the patients responded to conservative therapy with sedation, and supportive measures, and the use of electroshock. The third patient, after an illness of about one month, suddenly became severely ill, with high fever, shock, leukocytosis, and died suddenly. The cultural studies were all negative.

Intensive Chrysotherapy (With Lauron) in Rheumatoid Arthritis. *H. Harold Friedman and Otto Steinbrocker, New York, N. Y.* New England J. Med. 240: 362-66, March 10, 1949.

The results of intensive and accelerated gold therapy in 18 patients with active rheumatoid arthritis in various stages of the disease are reported. Sixteen patients were treated with aurothioglycanilide (lauron), one with aurothioglucose (solganol-B oleosum), and another with gold sodium thiomalate (myochrysine). The dosage ranged from 0.9 to 10 Gm. administered over a period of from 6 to 8 weeks in each case.

Of the 18 cases, 3 were early cases, 6 moderately advanced, and the remainder, greatly advanced. The disease process was active in all patients. Activity was determined by the presence of objective signs of joint inflammation and elevation of the erythrocyte sedimentation rate, which were present in all cases. Most of the patients, in addition, presented one or more of the following signs: low grade fever, leukocytosis, a moderately severe anemia, subcutaneous nodules, and tenovaginitis.

All patients had been under our observation for at least three months prior to chrysotherapy and had received the customary basic therapeutic measures employed for this disease, without objective evidence of improvement. Careful clinical and laboratory studies both before and during the course of treatment were done to detect toxicity. The results were evaluated according to the Criteria of the New York Rheumatism Association. The initial results, immediately after completion of the gold therapy, were as follows: complete remission of signs, 1 case; slight improvement, 2 cases; and no improvement, 15 cases. The patient who went into remission subsequently relapsed.

Complete remission of symptoms and signs occurred in 2 other patients 3 and 6 months respectively after intensive chrysotherapy, and each has maintained that status for 13 months. These may be regarded as initial, "delayed" responses, but may have been spontaneous.

Final evaluation of the series at the end of a follow-up period of from 8 to 18 months revealed the following: remission, 2 cases; slight improvement, 5 cases; and no improvement, 10 cases. (No follow-up study was obtained in one patient).

The toxic reactions in this series consisted only of one severe and one mild local exfoliative dermatitis. The patient with the severe exfoliative dermatitis, after a stormy course, made a complete recovery.

The use of large doses of gold salts over a short period in this series was not attended, therefore, by an increased number of toxic reactions, but the group is too small for any positive deductions regarding the safety of intensive chrysotherapy. On the whole, large and accelerated doses of aurothioglycanilide in these cases did not exert impressive palliative or suppressive effects on the signs and symptoms of rheumatoid arthritis. 9 references. 4 tables.—*Author's abstract.*

Roentgen Therapy of Rheumatic Spondylitis. *Nathan M. Spishakoff and B. V. A. Low-Beer, University of California Medical School, San Francisco, Calif.* California Med. 70: 124-29, Feb. 1949.

The treatment of spondylarthritis with x-rays dates from 1898, as first reported by Stenbeck and Sokolow. In this country, the pioneers were Anders, Daland and Pfahler, whose report appeared in 1906. However, the more widespread use of roentgen irradiation in the treatment of rheumatoid spondylitis is of more recent origin, following the stimulus of Smyth, Freyberg and Lampe, in 1941.

Etiology of the disease is not well understood, and it is classified by the American Rheumatism Association in the category "Probably Infectious (Etiology Not Known)", in which rheumatic fever, rheumatoid arthritis and Still's disease are also included.

Steinberg and Angevine have well described the underlying pathologic lesions. Following the initial development of synovial inflammation and edema, and infiltration of the subsynovial tissues by lymphocytes, monocytes and plasma cells, fibrinoid material, sometimes several layers thick, deposits over the synovial lining of the involved joints. A vascular granulation tissue pannus, originating in the perichondrium, then cloaks the surface of the articular cartilage, resulting in disturbed nutrition and eventful disintegration of the cartilage, after which fibrous ankylosis and even bony fusion between the opposing articular surfaces may occur.

In the attempt to control the crippling effects of the disease, which may, and often does, render its victim a social and economic liability, a variety of technics, using x-ray beams of diverse physical qualities have been employed.

The joints of the spine attacked by the disease lie at an approximate depth of 6 to 7 cm. beneath the skin. Isodose curves applicable to the beam and field size used in the Scott "wide-field" method indicate a depth dose of approximately 40% in the center of the field, diminishing to less than 10% at the periphery. Most of the other technics also result in uneven distribution of the radiation along the spine.

The method of treatment developed at the University of California Hospital has gradually evolved from treatment locally to painful areas, usually the lower spine, to a procedure utilizing relatively small fields placed

along the entire spine. The beam is generated by 200 KV constant potential, HVL 1.05 mm. copper, and used at 50 cm. distance. Four to five fields, measuring 10x10 to 10x15 cm. are designated along the longitudinal axis of the spine, including a single field placed transversely across the sacro-iliac joints. The close approximation of such fields results in practically homogeneous irradiation of the spine, as indicated by sagittal plane isodose curves, with a depth dose of approximately 50 to 55% throughout.

Treatment is given to the upper and lower halves of the spine on alternate days, so that 600 r (air) is delivered to each field in a period of 6 days. An identical course of therapy is repeated after a rest period of 4 weeks, and again after a second rest period of 12 weeks.

Since 1941, 167 cases have undergone treatment, 42 of which were excluded from the reported series because of incomplete data. Of the remaining 125, three courses of therapy were given to 73, with symptoms not relieved or recurring in 10 (13.8%). In the group of 35 cases receiving only two courses, 13 (37.1%) suffered recurrence or lack of relief. Six of 11 cases (54.5%) responded poorly when given only a single course of therapy, and all cases in whom treatment was given only to the lower back required subsequent therapy to the entire spine.

Complications of, and contraindications to treatment are relatively minor. Treatment should be withheld in the presence of leukopenia. Similarly, the possibility of menstrual dysfunction, or, on occasion, permanent amenorrhea in females must be considered. The gastro-intestinal disturbances which may be concomitant are temporary and transient and usually easily controlled by appropriate medical management.

The end results are most gratifying to the patient, however, since even the most advanced case may be relieved of pain and muscle spasm, while increased mobility of the spine and the thoracic cage is also regained by those in whom fixation and ankylosis has not occurred, following homogeneous irradiation of the entire spine, given in three courses with properly spaced intervening rest periods. 16 references. 3 tables. 4 figures. —*Nathan M. Spishakoff.*

12. Miscellaneous

Some Pharmacological Actions of Paludrine. *J. R. Vane, University of Oxford, Oxford, England.* Brit J. Pharmacol. 4: 14-21, March 1949.

Paludrine antagonised the action of acetylcholine or of vagal stimulation in most experiments: contractions of the isolated frog rectus muscle and of guinea pig ileum induced by acetylcholine were inhibited by paludrine (2×10^{-6}) and the normal action of acetylcholine on isolated rabbit auricles was abolished. The effects of vagal stimulation on the cat intestine in situ

and on the rabbit respiration were also reduced, as was the natural tonus of the intestine (1-20 mg. i.v.). Only on one preparation (the frog rectus muscle)was a stimulant action observed: low concentrations of paludrine (2×10^{-5}) potentiated acetylcholine contractions whereas in high concentrations (2×10^{-4}) the muscle contracted spontaneously. As with other drugs which antagonise acetylcholine, paludrine lengthened the refractory period of auricular tissue and by Dawes' method was found to be about eight times less active than quinidine. Contractions of the cat gastrocnemius and the rat diaphragm muscle, evoked by maximal nerve stimulation, were reduced by paludrine: this curare-like action was also demonstrated on the perfused superior cervical ganglion preparation of the cat. Large doses of paludrine (up to 80 mg.) reduced or abolished the vasoconstrictor action of adrenaline in the perfused hindleg of the dog and in the cat.

The antihistamine agents benadryl and neoantergan reduced the vasodilatation produced by paludrine (1-4 mg.) in the perfused hindleg of the dog and in the cat, suggesting that paludrine might release histamine from the tissues. The whole relationship between paludrine and histamine is difficult to understand, for whereas paludrine potentiated the constrictor effect of histamine on the guinea pig lungs, it inhibited gastric secretion in the cat and in man. (Burn, J. H. and Vane, J. R. *Brit. J. Pharmacol.* 3: 341, 1949; Vane, J. R., Walker, J. M. and Wynn Parry, C. W. *Brit. J. Pharmacol.* 3: 346, 1949.) It also inhibited contractions of isolated guinea pig ileum evoked by histamine. The L.D.50 of paludrine in mice agreed with figures of other workers and the delayed toxicity following intravenous injection in mice was also noted. The proportion of immediate deaths was greatly increased by simultaneous injection of prostigmine in a dose which itself caused no deaths. 31 references. 2 tables. 6 figures.—*John R. Vane.*

Roentgentherapy of Pain. *Origène Dufresne, Radium Institute, Montreal, Que., Canada.* Canad. M. A. J. 60: 227-29, March 1949.

Treatment of pain by roentgen rays is almost as ancient as roentgenology itself. Pain is a disagreeable sensation awakened by external or internal irritation of the sensory branches of the nerves. Painful sensations may be transmitted not only by sensory fibres belonging to our relation system, but also by some fibres belonging to our vegetative system.

Pain may be caused by: a) Mechanical irritation, b) inflammatory irritation of nerve sheathes, c) physical irritation, d) chemical irritation, e) infectious irritation.

Two theories can be put forward to explain the sedative action of roentgen rays: (a) a direct action of roentgen rays on the excitability of the nervous endings and on the conductivity of nerves; (b) an indirect action of roentgen rays by humoral modification. In the former case, roentgen rays would relieve pain by a photo-electronic effect on nervous elements; while

in the latter case roentgen rays by destroying white cells, could produce the liberation of triphosphage of adenosine, a normal component of the nucleus that is a powerful vaso-dilator of the capillaries.

Indications for the use of roentgen rays in the treatment of pain are:

1. Inflammatory lesions such as carbuncles of the upper lip; gonorrheal arthritis of knee; rheumatic arthritis of hip, spine and knees; periarticular fibrositis.

2. Tumors such as cancerous metastases developed in bones or in lymphatic glands near the bones, especially metastases of Hodgkin's disease.

3. Vaso-motor disturbances.

4. Essential neuralgias such as facial, radial, cubital, or sciatic neuralgias.

The technique for the treatment of pains differs according to the cause of pain. Roentgentherapy is an effective method for the treatment of pain, with a scientific basis. Roentgentherapy is an inoffensive therapeutic procedure, quite often capable of giving permanent results. Roentgentherapy should be used much more often for the treatment of refractory pain.

Interest in the Use of an Absorption-Delaying Vehicle for the Administration of Opiates. *(Interet d'un véhicule retard en therapeutique opiacée). F. Siguier, R. Giudicelli, and C. Walter, Paris, France.* Progrès méd. 76: 223-224, May 10, 1948.

Polyvinylpyrrolidone (PVP) was employed originally as a substitute for blood or plasma, administered intravenously. This viscous material subsequently was found to retard very significantly the absorption of various drugs mixed with it prior to injection. In this capacity it has been employed extensively to retard the absorption of such agents as hormones (insulin), local anesthetics (procaine), antibiotics (penicillin), glucosides, barbiturates, and many others.

It has, however, never been tried to retard the absorption of opiates, particularly morphine, that has to be administered to patients with incurable disease and severe pain over long periods of time. In this particular circumstance such absorption-delaying compounds as PVP could be most useful, both to reduce the amount of nursing care necessary for the frequent injections and perhaps to delay the onset of addiction by reducing the amount of morphine necessary for control of pain.

The biological tests used for assay of morphine in various animals injected with PVP-morphine mixtures were not sufficiently accurate. In vitro determinations indicated that morphine in 20 per cent PVP passed much more slowly through semipermeable membranes than in plain aqueous solution.

The PVP-morphine mixtures were administered to 30 subjects suffering from severe pain from chronic disease, largely incurable metastatic neoplasm. The injections were well tolerated. The effects of the opiate were

markedly prolonged by PVP. This made it possible to reduce the number of necessary injections from an average of 4 per 24 hours with morphine sulfate in aqueous solution to an average of 1.5 per 24 hours with morphine-PVP mixtures. The total daily dose of the patients could likewise be reduced from an average of 42 mg. per 24 hours (aqueous) to an average of 28 mg. per 24 hours (PVP).

These points suggest strongly that the administration of opiates to patients with otherwise intractable pain can be performed in 20% PVP with many advantages over the plain aqueous solution. 7 references.

Arachnidism. Effect of Calcium Gluconate in Six Cases. *William E. R. Greer, Robert Dawson Evans Memorial, Boston, Mass.* New England J. Med. 240: 5-8, Jan. 6, 1949.

The syndrome following the bite of a black-widow spider is a definite clinical entity. That the bite of this spider, Latrodectus mactans, present in all but 7 states of the United States, is poisonous for man has been recognized for centuries. Before Bogen's review of the literature in 1936, there was much skepticism attached to the fact that such a small creature could produce terrifying generalized symptoms in man. He reported 380 cases with 17 deaths, in 18 states. The spider has been reported to be increasing greatly in numbers in the vicinity of human habitations. Knowledge of the clinical entity is important since many spider victims are subjected to needless operations because the symptoms often simulate acute abdominal emergencies. An appalling record of human suffering has been checked back to L. mactans and its prototypes.

L. mactans are cannibalistic, feeding on each other whenever the opportunity presents itself. The nickname "black widow" given to the female of the species arises from its habit of capturing and feeding on the much smaller male after he has served the ends of species preservation. The globose abdomen of the female stands out like a highly polished pearl. The body averages 1.27 cm. in length. Slender pointed legs when expanded have a span of from 3.8 to 5.1 cm. On the ventral surface of the abdomen there is a rich red marking resembling an hourglass. Dorsal to the spinnerets in the midline of the convex surface of the abdomen is an additional red marking. When cornered or compressed, as between skin and clothing, the spider bites in self-defense. The male is ignored as an etiologic factor of any importance because of its size, timidity and scarcity.

The potent nature of the venom is appreciated readily by observing a victim about an hour after a bite. The victim writhes in agony, is terror-stricken and expresses fears of death. The venom of the female of this species is fifteen times as potent as that of a rattlesnake. The venom is believed to be a toxalbumin with its most damaging activity on nerve endings; it is a thick, translucent, oily, lemon-yellow fluid, which is acid in reaction and from which a hemolysin and arachnolysin have been isolated.

The syndrome, as presented by 6 patients bitten by the black widow spider observed in a seven day period in a tropical area, usually followed a similar pattern. There is transient excruciating pain, rapid edema and redness of the skin at the site of the bite (in 2 cases the site could not be identified). After ten to fifteen minutes a burning sensation spread centrifugally from the site of the bite and soon involved the whole body; this passed off after twenty to thirty minutes. There was sudden abdominal pain, (often cramp-like, as in acute condition of the abdomen) and cramp-like pains in the legs, arms and back. There was a general feeling of weakness, restlessness, extreme anxiety, headache, nausea and vomiting, and burning of the soles of the feet (in bites of unknown types this symptom may be pathognomonic). A board-like abdomen, nontender to palpation, was present in each of these 6 cases. There was hypersensitivity of the skin, and the calf muscles were tender to palpation. Two patients were in profound shock with blood pressure unobtainable; the other 4 patients had normal or slightly elevated blood pressure. Motion of the extremities was limited by muscle spasm and flexion was a prominent feature. The temperature was normal or only slightly elevated, and the pulse was slow (80 or under in all cases). Examination of the blood showed a moderate leukocytosis, and the 2 patients presenting a picture of profound shock showed albuminuria.

The patients in this series were immediately given 10 cc. of 10 per cent calcium gluconate intravenously. Subsequently, they were given a saline infusion containing 10 cc. of 10 per cent calcium gluconate. An icebag was applied to the affected area. Relief was obtained in a short time in all cases and was followed by profound sleep. The patients were out of bed the next day and back to work on the fourth day. Even the two patients in profound shock responded. No morphine was used and antivenin was not available. Intravenous magnesium sulfate, until symptoms of spider poisoning disappear, has been recommended and seemed rational in cases in which hypertension was a prominent factor. Hypertonic glucose has been used with varying results. Morphine sulfate in heavy doses has frequently been relied upon for relief by some physicians. It is reasonable to suppose that convalescent serum would be effective in spider-bite poisoning. Antivenin L. mactans) is listed in *New and Nonofficial Remedies*. In the series reported in this article intravenous calcium gluconate was found to give it is believed that this is the best available therapy in conjunction with other supportive measures. 20 references. 1 table.—*Author's abstract.*

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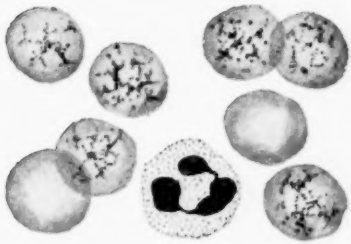

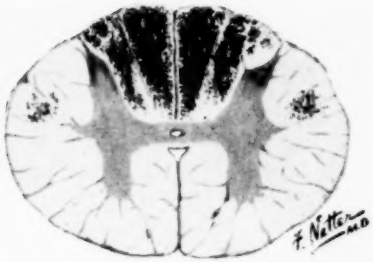

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